Joint session of the
Nonprescription Drugs Advisory Committee
and the
Endocrinology and Metabolic Drugs Advisory Committee

December 13, 2007

FDA Briefing Document

FDA Advisory Committee Briefing Document

Prepared by the Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
in collaboration with
Division of Metabolism and Endocrinology Products
December 13, 2007

NDA 21-213 proposing over-the-counter Mevacor™ (lovastatin) 20 mg

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DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the Review Division of Office. We have brought the issue of Mevacor™ as an over-the-counter product to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Discussion Points to Consider

Whether the overall benefit of having lovastatin available over-the-counter (OTC) outweighs the risk will be the focus of discussion at the advisory committee meeting. Thus, it will be important to focus your thinking on:

1. The labeling paradigms and whether one would be more appropriate than the other for an OTC lovastatin product and why

2. The label comprehension study data with an emphasis on comprehension of self-selection criteria, the pregnancy warning, and the muscle injury warning

3. The SELECT study self-selection data especially with regard to coronary heart disease risk, the population enrolled, pregnancy potential, reliance upon healthcare provider input to make a self-selection decision, and the behavior of those already taking a prescribed statin

4. How the data in the SELECT study bridges to the data in the CUSTOM study with respect to adherence, adverse events, and reaching the LDL target goal (since different labels were used)

5. The safety of lovastatin in consumers with chronic underlying liver disease

6. The role that an amyotrophic lateral sclerosis data mining signal, clinical trial data, and an ongoing case-control study on that topic should play in making a decision about statin availability OTC

EXECUTIVE SUMMARY

The intent of this Executive Summary is to provide background information and to raise points to consider as you prepare for the December 13, 2007 joint meeting of the Nonprescription Drug Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee. The purpose of the meeting is to address issues pertinent to the New Drug Application (NDA) to switch Mevacor (lovastatin) 20 mg from prescription to nonprescription marketing status. This meeting will be the third advisory committee meeting to consider this application, NDA 21-213. The first occurred on July 13, 2000 and the second on January 13 - 14, 2005. A few committee members scheduled to attend the December meeting have attended a previous meeting on this NDA; the majority of members have not.

This Background Package contains:

- Pertinent reviews (some of which have been presented at a prior advisory committee meeting on this NDA and some of which will be presented on December 13, 2007)
- Labels used in the consumer studies
- Communications between the FDA and Merck that provide a regulatory history of the development of Mevacor for over-the-counter (OTC) use
- References from the medical literature, including the current cholesterol treatment guidelines from the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII)
- The final report of the 2005 Advisory Committee meeting

Background:

1. Prescription to OTC Switch Process:

When considering whether or not it would be appropriate for lovastatin 20 mg to switch from prescription to OTC status it is important to recognize that the prescription to OTC switch process is guided by federal regulations. The Federal Food, Drug, and Cosmetic Act Sec. 201.[321](g)(1) states that the term "drug" means articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease and intended to affect the structure or any function of the body of man. The Durham-Humphrey Amendment to the Federal Food, Drug, and Cosmetic Act draws a distinction between prescription and non-prescription drugs. This distinction is stated in the Code of Federal Regulations 21 CFR 310.200(b) as follows:

"Any drug limited to prescription use under section 503(b)(1)(B) of the act shall be exempted from prescription-dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health by reason of the drug's toxicity or potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and he finds that the drug is safe and effective for use in self-medication as directed in proposed labeling."

When a drug that has been previously available only by prescription is switched to OTC status, the healthcare provider no longer serves as an intermediary to drug access. Thus,

to comply with 21CFR 310.200(b), it is necessary to take the indication, the target population, the safety concerns, and the behaviors that proper use of the drug demands of the consumer into account when considering whether a drug would be an appropriate candidate for nonprescription sale.

OTC Labeling

When you review the proposed OTC labeling for Mevacor 20 mg, bear in mind that the Code of Federal Regulations 21 CFR 201 Subpart C establishes labeling requirements for OTC Drugs. The regulations define what we can and cannot put on a product label and where we can put it. They describe the required elements of the principal display panel (often thought of as the front of the box) and of the Drug Facts. Among other things, the Drug Facts state, within the framework of the required "content and format" the active ingredient, its purpose, its use, warnings, and directions for use.

Consumer Studies Unique to the OTC Switch Process:

In this background package, you will find reviews of two new label comprehension studies:

- P087 Mevacor™ OTC Pivotal Select Label Comprehension Study
- P088 Mevacor™ OTC Muscle Warning Comprehension Study

There is one new self-selection study:

- P086 Self-Evaluation of Lovastatin to Enhance Cholesterol Treatment (SELECT)

There is one actual use study:

- A Consumer Use Study of OTC Mevacor™ (CUSTOM). The CUSTOM study was presented and reviewed at the 2005 advisory committee meeting. Please read this review because it is relevant to the discussion on December 13, 2007.

The following paragraphs will help to familiarize you with these types of consumer studies.

- What is a label comprehension study?

A label comprehension study determines whether a general population of potential users and non-users of the study drug can understand the information on a product label. No drug is administered. The study population is enriched with a low literacy cohort (whose literacy level has been determined by a validated literacy testing instrument) and sometimes with other cohorts of special interest. The study is a critical element to the label development process for an OTC drug and, if it succeeds, it demonstrates that respondents understand the tested label intended to accompany a product to market or that will be used in a self-selection study or an actual use study (see below). Label comprehension studies only test comprehension and may not accurately predict consumer behaviors (self-selection, purchase decisions, adherence, etc.).

A questionnaire designed to reflect the communication objectives of the study is the testing instrument. The questions should be well-designed so as to gather the appropriate information and not introduce bias. It is important to point out that a given study participant may technically answer a comprehension question incorrectly, but an explanation of the reasoning behind the response, may in fact, lead to a determination that

the answer is medically "acceptable." Thus, it is beneficial to ascertain why participants answer the way they do.

In NDA 21-213, label comprehension data demonstrated that consumers poorly comprehended the label that was used in the CUSTOM study particularly with regard to comprehension of cholesterol parameters. These data were discussed in detail at the January 13-14, 2005 advisory committee meeting. Subsequently, Merck developed new labeling that differs in many ways from the CUSTOM study label. As part of this process they conducted the two new label comprehension studies (P087 and P088) and the newly developed labeling was used in the SELECT study.

- What is a self-selection study?

A self-selection study determines if potential OTC users of a drug (some of whom could use the product and some of whom should not use the product), after reading the product label, correctly decide whether or not the product is appropriate for their personal use based upon the indications and warnings. A low literacy cohort and other subpopulations of interest are enrolled. No drug is administered.

This study assesses the ability of participants to correctly self-diagnose the condition for which the product is indicated. A meeting of the Nonprescription Drug Advisory Committee (NDAC) in September, 2006, focused on trial design issues for consumer studies for the OTC switch process. Committee members discussed that it might be useful, to analyze self-selection data based upon a pre-determined hierarchy of labeling information that would dictate success in self-selection. In other words, a ranking of importance (hierarchy) of certain labeling messages might be useful in determining success. In the discussion, the committee acknowledged that determining the hierarchies might be difficult.

Considering the newness of this thinking, it is not surprising that we have not yet seen a completed study that has used the hierarchy analysis approach. Hierarchies were not conducted *a priori* in the SELECT study since it was underway prior to this 2006 NDAC meeting. When you read Dr. Hu's review of the SELECT study, you will see that analyses based upon different hierarchies were performed after the data was collected. (You will also see that Merck used the term "self-assessment" to mean "self-selection.") No hierarchies were considered in the analysis of the CUSTOM study in 2005.

As a final point, analogous to label comprehension studies, it is important to understand the reasons why consumers answer the self-selection question incorrectly. Merck collected these reasons and they are considered in the data analyses.

- What is an actual use study?

The purpose of an actual use study is to simulate the OTC use of a product so we can attempt to predict if a drug would be used properly, safety, and effectively in the OTC setting. Study participants receive the product labeling and take the study drug home and use it. Often there is a study diary, but the concept behind a well-designed actual use

study is that the data collection methods should intrude as little as possible so as not to bias the study results.

The CUSTOM study was reviewed at the 2005 joint advisory committee meeting. This actual use study assessed many consumer behaviors:

- self-selection and the consumer's decision to purchase lovastatin,
- adherence (taking the drug and performing monitoring for efficacy and safety in accordance with the drug label)

The study was not placebo controlled, which is a common model for consumer behavior studies when behavior based upon one label design is being assessed. However, the CUSTOM study also provided some safety information (adverse events that occurred during the study) and efficacy information (the LDL-C response to treatment with lovastatin 20 mg in the consumers who used the product). No new actual use studies are provided for the December 13, 2007 meeting and therefore it will be important to consider how the data in the SELECT study bridges to the data in the CUSTOM study with respect to adherence, adverse events, and reaching the LDL target goal.

2. Hypercholesterolemia as an OTC Drug Indication

A brief recounting of the history of consideration of hypercholesterolemia as an OTC drug indication might be useful to committee members who are new to this issue. Since the mid-1990s there have been proposals for the nonprescription marketing of drugs to treat hypercholesterolemia. Initially, drugs in the bile-acid binding resin class were reviewed, but not approved. In 1997, the FDA issued a Guidance to Industry on Over-the-Counter Treatment of Hypercholesterolemia. The guidance was that hypercholesterolemia, a chronic, asymptomatic condition, required accurate diagnosis, risk assessment, and potentially clinical testing to prevent atherosclerotic cardiovascular disease and that the medical management should be directed by a healthcare professional. However, in 1999, FDA received two applications to switch statins OTC, one was for the lovastatin, and the other was for pravastatin. The Agency reviewed these applications and presented both of them to the July, 2000 joint advisory committee which recommended not approving both applications. Ultimately, in 2001, the Agency withdrew the 1997 Guidance, recognizing that the public interest in the availability of safe and effective therapies to treat hypercholesterolemia warranted communication between FDA and Industry to evaluate the feasibility of such therapies OTC. Formal and informal communications on this topic between FDA and industry have been ongoing ever since.

3. History of NDA 21-213 to Switch Lovastatin from Prescription to Nonprescription Status:

Lovastatin 20 mg has been marketed in the United States since 1987 as a prescription drug at doses of 20 mg a day to 80 mg a day. It is indicated for use as an adjunct to diet for the reduction of elevated total and LDL cholesterol in patients with primary hypercholesterolemia (Types IIa and IIb), when the response to diet restricted in saturated fats and cholesterol and to other non-pharmacological measures alone has been inadequate. It is also indicated to slow the progression of coronary atherosclerosis in

patients with coronary heart disease, as part of a treatment strategy to lower total and LDL cholesterol to target levels. Lovastatin is a Pregnancy Category X drug, because animal studies show fetal/neonatal adverse effects and there would not be a benefit to temporarily treating pregnant women with this drug. Thus, it is contraindicated during pregnancy. (Refer to the review by Dr. Karen Davis Bruno in the briefing package.)

In the original submission of NDA 21-213, Merck proposed that the appropriate OTC lovastatin dose would be 10 mg to treat their proposed OTC target population of consumers without clinically evident coronary heart disease but who were at risk because of mildly elevated cholesterol:

- Total cholesterol (Total-C) 200 – 240 mg/dL and
- LDL cholesterol (LDL-C) > 130 mg/dL

The July 2000 joint advisory committee considered the application and recommended that it should not be approved because of concerns about the inadequate lipid altering effectiveness of lovastatin 10 mg for the proposed target population. The committee also expressed concern that the applicant had not demonstrated, via multiple label comprehension and actual use studies, that OTC consumers could safely and appropriately self-manage their hypercholesterolemia.

On October 6, 2000, FDA sent Merck a letter stating that the NDA was deficient because "neither the rationale for treating the proposed target population with Mevacor 10 mg in the OTC setting, nor a favorable benefit/risk ratio for such treatment has been adequately established. Furthermore, the ability of consumers to appropriately self-select and to adequately comply with chronic Mevacor therapy without the intervention of a physician has not been demonstrated." The letter listed the following bases for these conclusions: The application did not:

- Provide sufficient evidence that consumers could use Mevacor 10 mg in accordance with the National Cholesterol Education Program (NCEP) guidelines
- Establish there is a clinical cardiovascular benefit of Mevacor 10 mg in the proposed OTC target population
- Establish a treatment goal and demonstrate that consumers could individualize their treatment to achieve the treatment goal without the intervention of a physician
- Demonstrate that consumers can adequately comprehend the complexities of treatment of hypercholesterolemia, can adequately self-select for OTC treatment and can adequately adhere with the chronic therapy required to obtain a clinically meaningful reduction in cardiovascular risk
- Adequately address safety concerns related to hepatic toxicity and rhabdomyolysis
- Adequately demonstrate that consumers comprehend the increased risks associated with concomitant use of lovastatin and other drugs metabolized by cytochrome P450 3A4 among which are serious muscle toxicity
- Adequately address how consumers will access cholesterol testing and other types of support that will assist in the OTC setting to encourage appropriate follow up testing

- Adequately address the risks to the fetus of potential use by women who are pregnant or of child bearing potential of this Pregnancy Category X drug

This letter is in your background package.

In 2004, Merck resubmitted NDA 21-213 with the intent to address the deficiencies delineated in the aforementioned letter. In the resubmission, they proposed, instead of the lovastatin 10 mg fixed daily dose, a lovastatin 20 mg fixed daily dose to treat the following proposed OTC population:

- Males ≥ 45 years or females ≥ 55 years
- LDL-C 130 – 170 mg/dL
- Having at least one of the following risk factors:
  - Smoking
  - HDL-C between 1 and 39
  - Family history of heart attack in father/brother before age 55 or mother/sister before age 65
  - High blood pressure

In the background package you will find reviews addressing the lipid altering efficacy of lovastatin 20 mg by Dr. Mary Parks and a statistical review of AFCAPS/TexCAPS by Dr. Parks and Ms. Mele. These reviews were part of the background package for the January, 2005 advisory committee meeting.

Please refer to the January, 2005 advisory committee meeting summary minutes in your background package as you read the following paragraphs. At that meeting, the joint committee agreed that the proposed target population merits treatment with a statin to lower cholesterol and thereby reduce heart disease along with improved diet and cholesterol. The committee agreed that the sponsor had provided an adequate rationale for the use of a fixed dose of lovastatin 20 mg to lower cholesterol and heart disease risk in this population, with the caveat that this is an effective dose to reduce cholesterol in this population assuming adherence to the label. Committee members were concerned that there is not enough data, especially for OTC use, of the efficacy of a 20 mg dose versus usual care.

The 2005 committee agreed that baseline liver function testing and liver function monitoring for Mevacor 20 mg were not necessary. The committee members generally found that the risk of liver toxicity with statins was low and were not excessively concerned with the use of lovastatin 20 mg by those with undiagnosed liver problems. The committee agreed that the risk of muscle toxicity with lovastatin 20 mg was acceptable for an OTC drug as applied to the population on the label. However, there was discussion that "the study indicated problems in the self-selection of patients for the use of lovastatin, which may cause some safety concerns."

On the issue of the Pregnancy Category X status of lovastatin, the majority of members (18 of 24) thought that they had heard data that suggests that the drug is not so potentially

toxic to the fetus to prevent its marketing OTC under any circumstances. However, all of the members agreed that the pregnancy warning on the proposed OTC label was not adequate.

The majority of committee members felt that the self-selection results from the CUSTOM study were not sufficient to support a conclusion that consumers can use lovastatin 20 mg safely and effectively in the OTC setting without the guidance of a physician. Committee members expressed concerns about the ability of OTC consumers to self-manage their cholesterol with regard to self-monitoring and drug interactions.

In February, 2005, FDA sent Merck a letter stating that the data in their resubmission was not approvable. This letter is in this background package. The letter stated "You have not provided sufficient evidence that you have defined labeling, packaging, and marketing proposals that would be sufficient to ensure that OTC consumers could properly assess the benefits, the risks, and the correct circumstances of use for Mevacor OTC. Furthermore, your overall program provides inadequate assurance that OTC consumers can successfully self-manage the complexities of treatment and follow up of the chronic, asymptomatic target condition in order to prevent cardiovascular disease." The letter commented that the actual use study, CUSTOM, suggested that most, but not all, subjects made satisfactory decisions with regard to the use of the product after self-selection. This was particularly evident in that approximately 70% of users had their LDL-C checked and 75% made a correct decision on whether to continue drug use. However, the response to the muscle pain warning was of concern and needed improvement. Specifically, FDA advised that Merck:

- Conduct a self-selection/use study or studies to demonstrate that consumers can make decisions with an understanding of their likelihood of benefits weighed against the risks of using lovastatin 20 mg. The agency encouraged the development of a simpler label.
- Develop labeling that accomplishes a demonstrably higher rate of compliance with the muscle toxicity warning since, in the CUSTOM study, only 75% of subjects who developed muscle pain made a correct decision about Mevacor use.
- Review their program and determine which aspects are essential to assist the consumer in making decisions on use of the product.
- Describe the measures that they are planning to take to ensure that promotion of Mevacor OTC is directed to the targeted population based on label criteria or provide assurance that promotional efforts will not engender open-market use patterns such that the results and conclusions of the self-selection studies may not be valid.
- Provide sufficient evidence that the risk of hepatotoxicity is minimal in patients with common asymptomatic liver diseases in order to support removal of the current recommendation to monitor hepatic transaminases or provide sufficient evidence that consumers can make clinical safety assessments of hepatic risks before initiating therapy with nonprescription lovastatin.

- Modify the label and test consumer comprehension and consumer self-selection to ensure adequate consumer understanding of the risks of drug exposure during pregnancy.

Merck re-submitted their application in July, 2007. They have provided new labeling that has been tested in two label comprehension studies, a new self-selection study (SELECT), additional safety data, including data assessing the safety of lovastatin use in those with underlying chronic liver disease, "Study of Potential Hepatotoxicity of Lovastatin in the Northern California Kaiser Permanente Liver Disease Population." (The labels and reviews of the consumer studies and new safety data are in your background package.)

Refer to the labels in the background package. The new labeling submitted, in fact, consists of two labeling paradigms. One label is based upon an LDL-C paradigm. The LDL-C paradigm targets the same OTC population studied in the CUSTOM study and presented at the January, 2005 Advisory Committee Meeting. That label differs in format and in content, especially with respect to warnings from the CUSTOM label.

The other label is based upon a Total-C paradigm both for self-selection and treatment goal. Merck chose to test this label based upon their analyses of surveys that they state indicate that consumers are more familiar with the term "total cholesterol" than with "LDL cholesterol." As such, the Total-C label is quite different from that used in the CUSTOM study.

Both new labeling paradigms were tested in the comprehension and SELECT studies. Both labels now list specific medications which can interact with lovastatin; the label used in the CUSTOM study did not.

It should be pointed out that at an April 25, 2005 meeting with Merck, the Agency confirmed that the treatment paradigm must be consistent with the NCEP ATP III Guidelines, which use LDL-cholesterol as the basis for determining therapy. The minutes from that meeting are in your package.

Points to Consider:
Whether the overall benefit of having lovastatin available OTC outweighs the risk will be the focus of discussion at the advisory committee meeting. Thus, it will be important to focus your thinking on:

1. The labeling paradigms and whether one would be more appropriate than the other for an OTC lovastatin product and why
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3. The SELECT study self-selection data especially with regard to coronary heart disease risk, the population enrolled, pregnancy potential, reliance upon healthcare provider input to make a self-selection decision, and the behavior of those already taking a prescribed statin

4. How the data in the SELECT study bridges to the data in the CUSTOM study with respect to adherence, adverse events, and reaching the LDL target goal (since different labels were used)
5. The safety of lovastatin in consumers with chronic underlying liver disease
6. The role that an amyotrophic lateral sclerosis data mining signal, clinical trial data, and an ongoing case-control study on that topic should play in making a decision about statin availability OTC

Andrea Leonard-Segal, M.D.
Director, Division of Nonprescription Clinical Evaluation
November 12, 2007

Once-a-day

MEVACOR™ OTC

Lovastatin 20 mg
CHOLESTEROL REDUCER

- For people with elevated LDL "bad" cholesterol between 130–170 mg/dL
- To reduce LDL cholesterol to 129 or below and keep it down

45 TABLETS

Read back for more information

Drug Facts (continued)

Inactive ingredients Butylated hydroxyanisole (BHA), cellulose, FD&C blue No. 2 aluminum lake, lactose, magnesium stearate, and starch.

Other information See inside package for additional information or talk to the study personnel. If after buying this product you decide it is not right for you, return it for a full refund.

Distributed by:
Johnson & Johnson • Merck
CONSUMER PHARMACEUTICALS CO.
FORT WASHINGTON, PA 19034 USA

LOT NO. WP-K263
EXP. 03FEB2004

Read the warnings and directions before use.
Store at 5°-30° C (41°- 86° F). Protect from light.

8/18/70

MEVACOR™ OTC
Once-a-day
Lovastatin 20 mg
CHOLESTEROL REDUCER

Caution: New Drug – Limited by Federal (USA) Law to Investigational Use.

Drug Facts

Active ingredient (in each tablet) — **Purpose**

Lovastatin 20 mg ..... Cholesterol reducer

Use To help lower LDL "bad" cholesterol, which may prevent a first heart attack. This product is for people who meet the requirements in the sections below.

Warnings

Do not use if

- **Liver disease:** Do NOT use if you have liver disease.
- Do NOT use if you have had any muscle pain, weakness or tenderness from taking a cholesterol-lowering medicine.
- **Pregnant or breast-feeding:** Do NOT use if you are pregnant or breast-feeding.
- **Allergic to lovastatin:** Do NOT use if you know you are allergic to lovastatin or the inactive ingredients in this medicine, as listed below.

Ask your doctor or pharmacist (study personnel) before use if you are taking

- Any prescription medicine: If you are taking any prescription medicine, ask your doctor or study personnel before taking MEVACOR™ OTC. Certain drugs can interact with MEVACOR™ OTC and can increase the possibility of side effects.
- Other cholesterol-lowering medicine: Do NOT substitute MEVACOR™ OTC for your prescription or non-prescription cholesterol-lowering medicine without talking to your doctor.
- New prescriptions: Tell your doctor you are taking MEVACOR™ OTC before you begin taking any new prescription medicine.

Do NOT use unless directed by your doctor if you have

- very high LDL "bad" cholesterol 171-400 mg/dL
- high triglycerides 200-900 mg/dL
- healthy HDL "good" cholesterol 60-200 mg/dL
- had a stroke
- ever had heart disease (heart attack or angina)
- diabetes

Stop use and ask the study doctor if you develop any unexplained muscle pain, weakness or tenderness. Stop use immediately. This can be a sign of a rare but serious side effect.

If you are diagnosed with a new medical condition, tell your doctor you are taking MEVACOR™ OTC.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

How to decide if MEVACOR™ OTC is right for you

Before using you must have

- Tried a healthy diet and exercise to reduce your cholesterol.
- Had a fasting cholesterol test within the last year. If you do not know your numbers, call your doctor to get them or get a new test.

Who can use: You must have YES (blue) answers to all 4 of the following. Total cholesterol is important, but you must know your exact fasting LDL and HDL numbers.

1 MEVACOR™ OTC is **only** for men 45 years or older **AND** women 55 years or older

Yes, I am a man 45 or older or a woman 55 or older – continue ▶

Men 44 or younger or women 54 or younger
STOP **Do not use - ask your doctor or study personnel.**

2 MEVACOR™ OTC is **only** for people with LDL "bad" cholesterol between **130 – 170 mg/dL**

Yes, my LDL before use is 130-170 mg/dL – continue ▶

Between 1-129 mg/dL or 171-400 mg/dL or don't know
STOP **Do not use - ask your doctor or study personnel.**

3 MEVACOR™ OTC is only for people with one or more of these conditions that increase heart risk:
(If yes to any, you may need MEVACOR™ OTC.)

- ▶ You are a smoker **(may need MEVACOR™ OTC) OR**
- ▶ HDL "good" cholesterol 1-39 mg/dL **(too low) OR**
- ▶ Heart attack or angina in father or brother before 55; mother or sister before 65 **OR**
- ▶ High blood pressure

Yes, I have one or more of the above – continue ▶

I have none of the above or I'm not sure/don't know
STOP **Do not use - ask your doctor or study personnel.**

4 MEVACOR™ OTC is only for people who are free of **ALL** conditions in the ***Warnings*** section above

Yes, I am free of all *Warnings* above – continue ▶

I have a condition listed in ***Warnings*** section or don't know
STOP **Do not use - ask your doctor or study personnel.**

I have all YES (blue) answers. I can use MEVACOR™ OTC see directions below.

I have a STOP answer I cannot use.

Directions

1 Take one tablet daily:

- If you stop taking MEVACOR™ OTC, your cholesterol will go back up.
- For best results, take it with the evening meal. (Your body makes more cholesterol at night.)
- Continue to eat a healthy diet and exercise.
- Do not take more than one tablet per day.

2 Test at 6 weeks: See if your LDL test result is 1-129 mg/dL: "YES" or "NO"?

- **NO –** If at 6 weeks your LDL "bad" cholesterol is higher than 129 mg/dL, STOP stop taking MEVACOR™ OTC. Talk to the study doctor or study personnel. MEVACOR™ OTC may not be enough for you.
- **YES –** If at 6 weeks your LDL "bad" cholesterol is 1-129 mg/dL, it's working, keep taking it daily and test your cholesterol once a year. If you stop, your cholesterol will go back up.
- For information on cholesterol testing, talk to the study personnel.

3 Talk to your doctor if there is a change in your health:

- New prescriptions: Tell your doctor you are taking MEVACOR™ OTC before you begin taking any new prescription medicine.
- New medical condition: If diagnosed with a new medical condition, tell your doctor you are taking MEVACOR™ OTC.
- Unexplained muscle pain: Stop use immediately and talk to the study doctor if you develop any unexplained muscle pain, weakness or tenderness. This can be a sign of a rare but serious side effect. ▼

PROPOSED PACKAGE LABEL (LDL)

FRONT PANEL

SCALE 100%

PROPOSED PACKAGE LABEL (LDL)

OUTSIDE PANEL

Labeling Format Information:

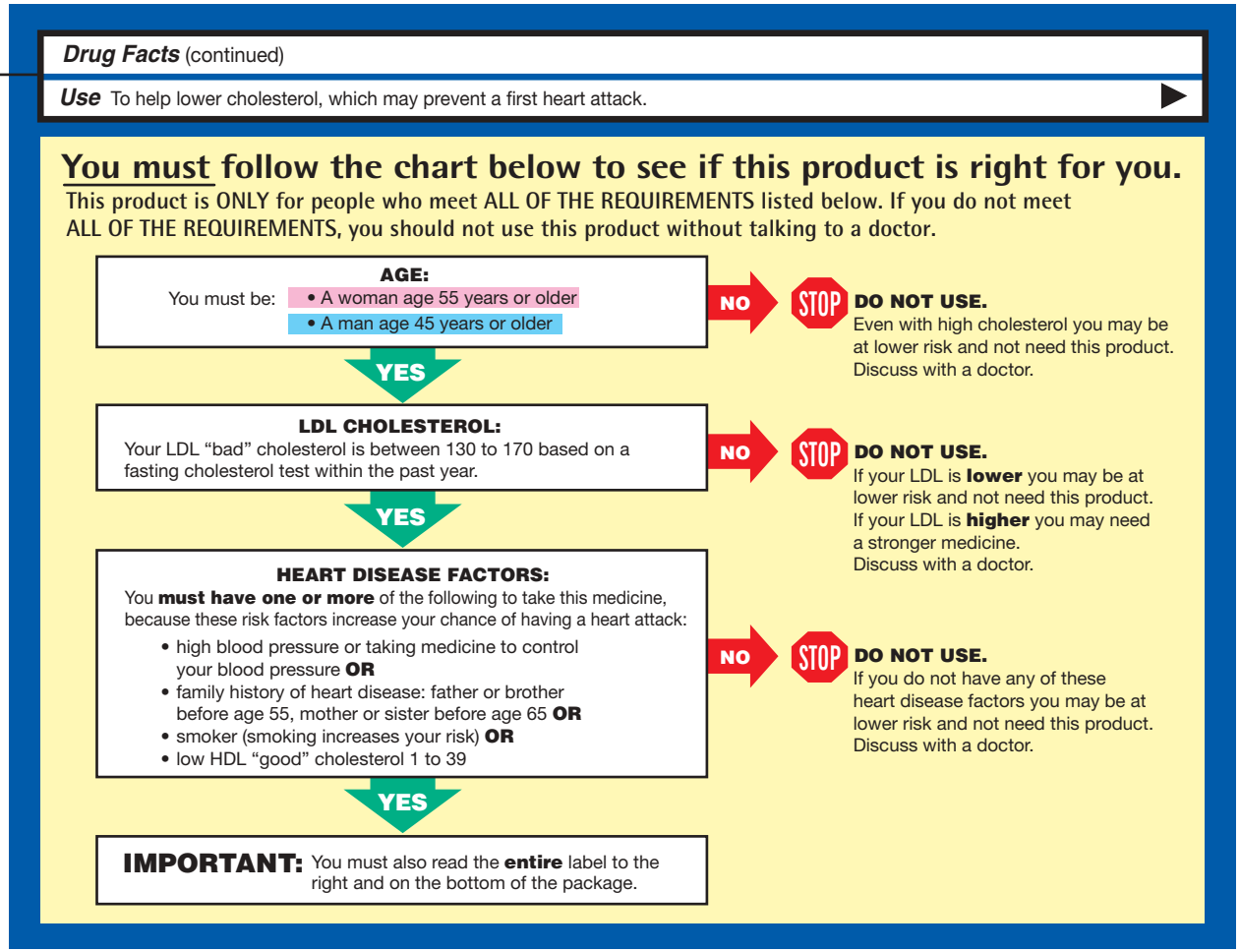
Fonts: Helvetica roman, bold oblique

Drug Facts:	14 pt	**Body Text Leading**:	9 pt
Header:	9 pt	**Barlines**:	2.5 pt
Body Text:	7pt	**Hairlines**	.5 pt
Avg Horizontal Scale: 100%		Avg Kerning: 0	

SCALE 100%

PROPOSED PACKAGE LABEL (LDL)

INSIDE FLAP – PANEL ON LEFT



Labeling Format Information:

Fonts: Helvetica roman, bold oblique, black

Drug Facts:	14 pt	**Body Text Leading**:	8.5 pt
Header:	9 pt	**Barlines**:	2.5 pt
Body Text:	7 pt	**Hairlines**	.5 pt
Avg Horizontal Scale: 100%		Avg Kerning: 0	

SCALE 100%

PROPOSED PACKAGE LABEL (LDL)

INSIDE FLAP – PANEL ON RIGHT

Drug Facts (continued)

Warnings

Do not use if you know you are allergic to lovastatin

Ask a doctor before use if you

- are taking prescription cholesterol medicines. Do not substitute. This product is probably not strong enough for you
- have LDL "bad" cholesterol 171 to 400. You are at higher risk for heart disease
- are a woman under age 55 or a man under age 45. You may be at lower risk for heart disease
- are a woman with high HDL "good" cholesterol 60 to 200. You may be at lower risk for heart disease
- have liver disease
- have had heart disease
- have had a stroke
- have diabetes

Ask a doctor or pharmacist before use if you are

- unsure of your cholesterol numbers or have not had a fasting cholesterol test within the last year
- taking any of the following, as certain drugs or foods can cause interactions:
  - cholesterol medicines
  - oral antibiotics
  - oral antifungals
  - drugs for irregular heartbeat
  - HIV protease inhibitors
  - cyclosporine (immune suppressant)
  - nefazodone (antidepressant)
  - large quantities of grapefruit juice (more than 1 quart daily)

When using this product, talk to a doctor if there is a change in your health, such as a new prescription medicine or a new medical condition.

Stop use and ask a doctor if you develop any unexplained muscle pain, weakness or tenderness.
This can be a sign of a rare but serious side effect.

If pregnant or breast-feeding, or think you may become pregnant, do not use. This product may cause problems in the unborn child.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- this product is only for you if
  - you are a woman 55 years or older or a man 45 years or older and
  - your LDL "bad" cholesterol is between 130 and 170 and
  - you also have one or more of the following heart disease factors which increase your chance of a heart attack:
    - high blood pressure or taking medicine to control your blood pressure or
    - family history of heart disease: father or brother before age 55, mother or sister before age 65 or
    - smoker (smoking increases your risk) or
    - low HDL "good" cholesterol 1 to 39

▼ READ LABEL WARNINGS CAREFULLY ▼

LIFT ◀ HERE

Labeling Format Information:

Fonts: Helvetica roman, bold oblique, black

Drug Facts:	14 pt	**Body Text Leading**:	7.5 pt
Header:	9 pt	**Bullets**	6 pt
Subheader:	7.5 pt	**Barlines**:	2.5 pt
Body Text:	7 pt	**Hairlines**	.5 pt

Avg Horizontal Scale: 100% Avg Kerning: 0

SCALE 100%

PROPOSED PACKAGE LABEL (LDL)

BOTTOM PANEL

Drug Facts (continued)

Directions (continued)

- take only one tablet daily with your evening meal (your body makes more cholesterol at night)
- continue to eat a healthy diet and exercise
- after 6 weeks get a fasting cholesterol test to see if your LDL "bad" cholesterol has reached a healthy level:
  - LDL "bad" cholesterol 1 to 129. It's working, keep taking it daily and test your cholesterol once a year
  - LDL "bad" cholesterol 130 to 400. This product may not be strong enough for you. Talk to a doctor about using a prescription cholesterol medicine
- if you stop taking this product, your cholesterol will go back up

Other information

- before using this product, you must have tried a healthy diet and exercise to reduce your cholesterol
- before using this product, read the materials enclosed in this package for additional important information
- store at 5°-30° C (41°-86° F)

Inactive ingredients Butylated hydroxyanisole (BHA), cellulose, FD&C blue No. 2 aluminum lake, lactose, magnesium stearate, and starch

Questions? Call toll-free 1-800-_____ from __a.m. to __p.m. (ET) Monday to Friday or visit our website anytime at www.xxxxxxx.com

Labeling Format Information:

Fonts: Helvetica roman, bold oblique, black

Drug Facts:	14 pt	**Body Text Leading**:	7.5 pt
Header:	9 pt	**Bullets**	6 pt
Subheader:	7.5 pt	**Barlines**:	2.5 pt
Body Text:	7 pt	**Hairlines**	.5 pt

Avg Horizontal Scale: 100% Avg Kerning: 0

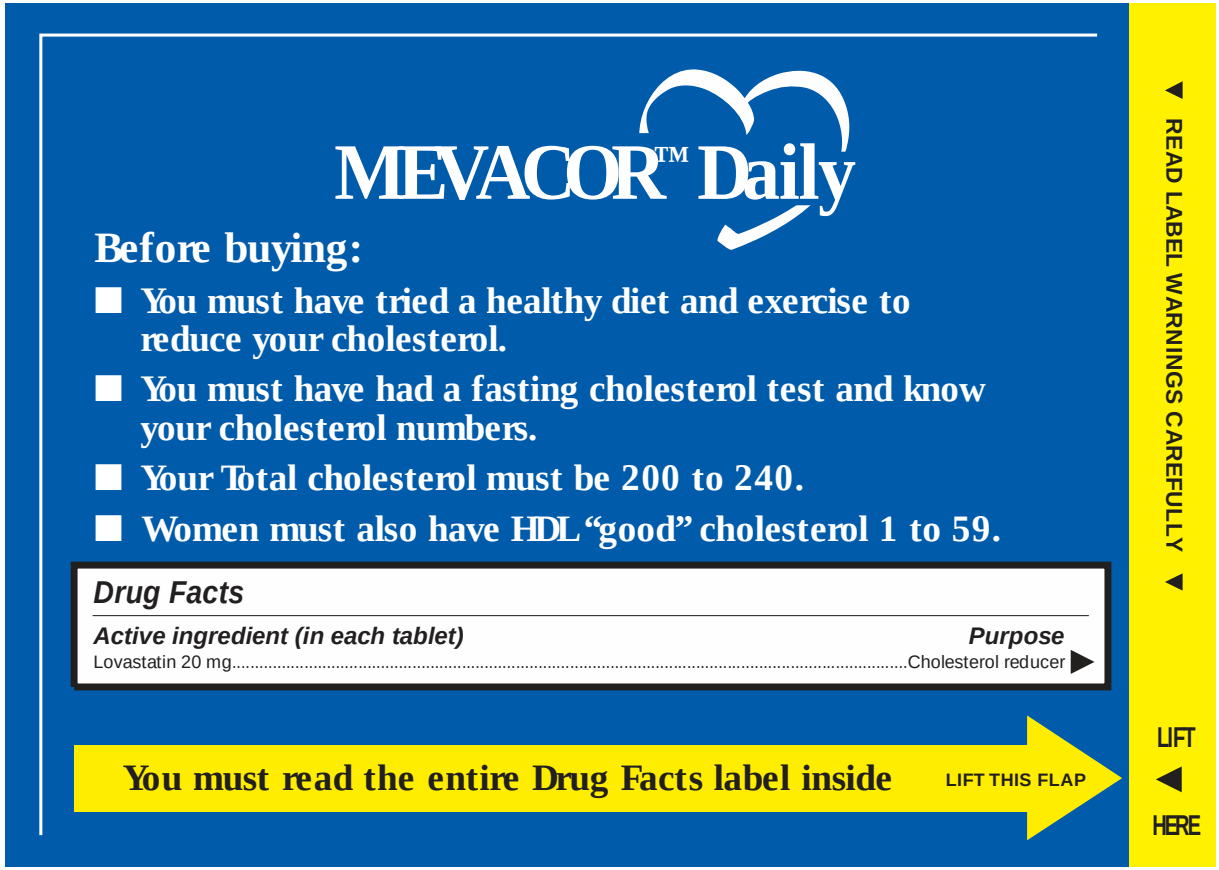
SCALE 100%

SELECT Package Label (TOTAL)

FRONT PANEL

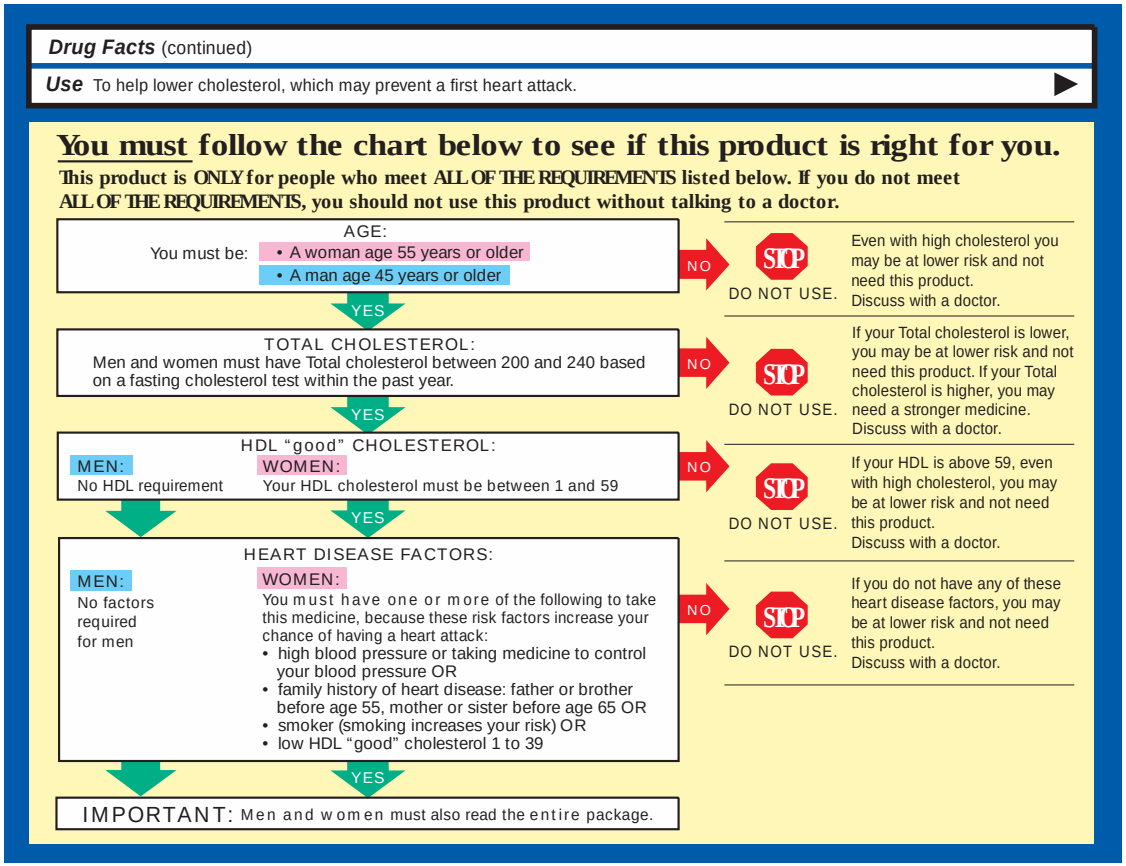
SELECT Package Label (TOTAL)

OUTSIDE PANEL



SELECT Package Label (TOTAL)

INSIDE FLAP – PANEL ON LEFT



Drug Facts (continued)

Use To help lower cholesterol, which may prevent a first heart attack.

You must follow the chart below to see if this product is right for you.

This product is ONLY for people who meet ALL OF THE REQUIREMENTS listed below. If you do not meet ALL OF THE REQUIREMENTS, you should not use this product without talking to a doctor.

AGE:
You must be:
- A woman age 55 years or older
- A man age 45 years or older

NO → STOP DO NOT USE. Even with high cholesterol you may be at lower risk and not need this product. Discuss with a doctor.

YES

TOTAL CHOLESTEROL:
Men and women must have Total cholesterol between 200 and 240 based on a fasting cholesterol test within the past year.

NO → STOP DO NOT USE. If your Total cholesterol is lower, you may be at lower risk and not need this product. If your Total cholesterol is higher, you may need a stronger medicine. Discuss with a doctor.

YES

HDL "good" CHOLESTEROL:

MEN: No HDL requirement

WOMEN: Your HDL cholesterol must be between 1 and 59

NO → STOP DO NOT USE. If your HDL is above 59, even with high cholesterol, you may be at lower risk and not need this product. Discuss with a doctor.

YES

HEART DISEASE FACTORS:

MEN: No factors required for men

WOMEN: You must have one or more of the following to take this medicine, because these risk factors increase your chance of having a heart attack:
- high blood pressure or taking medicine to control your blood pressure OR
- family history of heart disease: father or brother before age 55, mother or sister before age 65 OR
- smoker (smoking increases your risk) OR
- low HDL "good" cholesterol 1 to 39

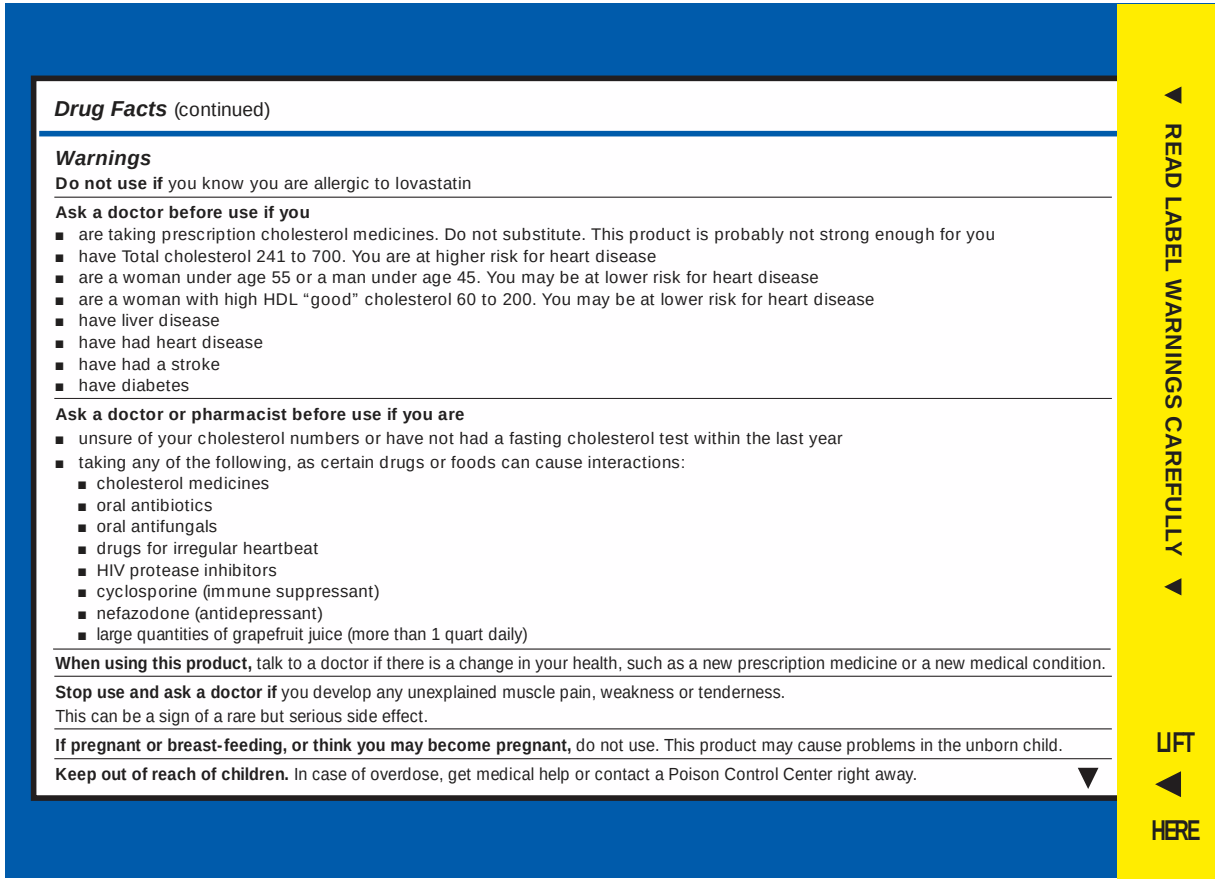
NO → STOP DO NOT USE. If you do not have any of these heart disease factors, you may be at lower risk and not need this product. Discuss with a doctor.

YES

IMPORTANT: Men and women must also read the entire package.

SELECT Package Label (TOTAL)

INSIDE FLAP – PANEL ON RIGHT



Drug Facts (continued)

Warnings

Do not use if you know you are allergic to lovastatin

Ask a doctor before use if you

- are taking prescription cholesterol medicines. Do not substitute. This product is probably not strong enough for you
- have Total cholesterol 241 to 700. You are at higher risk for heart disease
- are a woman under age 55 or a man under age 45. You may be at lower risk for heart disease
- are a woman with high HDL "good" cholesterol 60 to 200. You may be at lower risk for heart disease
- have liver disease
- have had heart disease
- have had a stroke
- have diabetes

Ask a doctor or pharmacist before use if you are

- unsure of your cholesterol numbers or have not had a fasting cholesterol test within the last year
- taking any of the following, as certain drugs or foods can cause interactions:
  - cholesterol medicines
  - oral antibiotics
  - oral antifungals
  - drugs for irregular heartbeat
  - HIV protease inhibitors
  - cyclosporine (immune suppressant)
  - nefazodone (antidepressant)
  - large quantities of grapefruit juice (more than 1 quart daily)

When using this product, talk to a doctor if there is a change in your health, such as a new prescription medicine or a new medical condition.

Stop use and ask a doctor if you develop any unexplained muscle pain, weakness or tenderness.
This can be a sign of a rare but serious side effect.

If pregnant or breast-feeding, or think you may become pregnant, do not use. This product may cause problems in the unborn child.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

▼ READ LABEL WARNINGS CAREFULLY ▼

LIFT ◀ HERE

SELECT Package Label (TOTAL)

BOTTOM PANEL

Drug Facts (continued)

Directions

This product is only for

- Men
  - you are 45 years or older and
  - your Total cholesterol is between 200 and 240
- Women
  - you are 55 years or older and
  - your Total cholesterol is between 200 and 240 and
  - your HDL "good" cholesterol is between 1 and 59 and
  - you must also have one or more of the following heart disease factors which increase your chance of a heart attack:
    - high blood pressure or taking medicine to control your blood pressure or
    - family history of heart disease: father or brother before age 55, mother or sister before age 65 or
    - smoker (smoking increases your risk) or
    - low HDL "good" cholesterol 1 to 39

- take only one tablet daily with your evening meal (your body makes more cholesterol at night)
- continue to eat a healthy diet and exercise
- after 6 weeks get a fasting cholesterol test to see if your Total cholesterol has reached a healthy level:
  - Total cholesterol 1 to 199. It's working, keep taking it daily and test your cholesterol once a year
  - Total cholesterol 200 to 700. This product may not be strong enough for you. Talk to a doctor about using a prescription cholesterol medicine
- if you stop using this product, your cholesterol will go back up

▶

Drug Facts (continued)

Other information

- before using this product, you must have tried a healthy diet and exercise to reduce your cholesterol
- before using this product, read the materials enclosed in this package for additional important information
- store at 5˚- 30˚C (41˚- 86˚F)

Inactive ingredients Butylated hydroxyanisole (BHA), cellulose, FD&C blue No. 2 aluminum lake, lactose, magnesium stearate, and starch.

Questions? Call toll-free 1-800-_____ from __a.m. to __ p.m. (ET) Monday to Friday or visit our website anytime at www.xxxxxxx.com

FRONT

PACKAGE INSERT

IMPORTANT INFORMATION ABOUT MEVACOR™ Daily (Lovastatin 20 mg).
PLEASE READ THIS PACKAGE INSERT AND SAVE FOR FUTURE USE.

MEVACOR™ Lovastatin 20 mg CHOLESTEROL REDUCER Daily

What is MEVACOR™ Daily?
MEVACOR™ Daily contains an ingredient that has been used for over 20 years by millions of people to lower their cholesterol. MEVACOR™ Daily should be used to help lower your LDL cholesterol as part of a total heart healthy program, including eating a low-fat, low-cholesterol diet and exercising. This program may reduce your risk of suffering a first heart attack or stroke.

What is cholesterol and why can it be a problem?
Cholesterol is a fat-like substance that is made in your liver, and can be found in food that you eat. Your body needs cholesterol to survive (to build cells, for example), but too much of it can cause problems. It can build up in your arteries and make it harder for your blood to flow. When this happens in the arteries of your heart, it can cause chest pain (angina), or if the artery becomes totally blocked, a heart attack. High cholesterol may be due to many factors and often runs in families. These factors include eating too much food high in saturated fats, hereditary conditions, and certain illnesses such as thyroid or kidney disease.

What are LDL and HDL cholesterol?
Cholesterol comes in two main forms, LDL and HDL. LDL cholesterol can build up in your arteries; this is why it is considered the "bad" cholesterol. HDL is considered "good" cholesterol because it helps remove the "bad" cholesterol from your arteries. An easy way to think of HDL is "H" for Healthy. For good heart health, just remember that LDL levels should be Low and HDL levels should be High. Total cholesterol is made up of LDL and HDL cholesterol, and other blood fats, so people with high total cholesterol tend to have high LDL cholesterol as well.

How does MEVACOR™ Daily work?
MEVACOR™ Daily helps your liver produce less cholesterol. As a result, MEVACOR™ Daily reduces the level of LDL "bad" cholesterol in the blood. Because your body makes cholesterol every day, you need to take MEVACOR™ Daily every day to control it. With continued use, MEVACOR™ Daily can help you keep your cholesterol down, which could lead to a healthier heart.

What are the side effects of MEVACOR™ Daily?
The active ingredient in MEVACOR™ Daily has been generally well-tolerated. Side effects have usually been mild. However, as with most drugs, serious side effects may occur. If the following or any other side effects occur while taking MEVACOR™ Daily, stop use and talk to your doctor right away.

- **Stop using and tell your doctor right away if you develop new or unusual muscle pain, tenderness or weakness that you can't explain (especially if you have a fever or feel ill). This is because on rare occasions, muscle problems can be serious, including muscle breakdown resulting in kidney damage. This side effect can occur even if you have been on MEVACOR™ Daily for a long period of time.**

Things you can do to have a healthy heart

- **Eat a low-fat, low-cholesterol diet** – Avoiding high-fat foods can help you lower your cholesterol, including your LDL "bad" cholesterol.
- **Exercise** – Exercising three or more times a week may reduce your chances of having heart disease. Talk to your doctor before starting any exercise program.
- **Quit smoking** – Smoking is another problem for your heart. Although smoking does not raise your cholesterol, it increases your risk for heart attack, stroke, and cancer.
- **Lower your blood pressure if it is too high** – High blood pressure increases your risk for heart attack or stroke. Have your blood pressure checked regularly. If blood pressure medicine is prescribed for you, remember to take it.

Before using MEVACOR™ Daily, you should carefully read the back of the package and this package insert to determine if MEVACOR™ Daily is right for you.

Before using, you must have

- Tried a healthy diet and exercise to reduce your cholesterol.
- Had a fasting cholesterol test within the last year. If you do not know your numbers, call your doctor to get them or get a new test.

If you are not sure if MEVACOR™ Daily is right for you, talk to your doctor or pharmacist or call 1-800-XXX-XXXX to reach a product specialist or visit us on the web at www.xxxxxxx.com.

8¼"

6¾"

Labeling Format Information:

Fonts: Helvetica roman, bold, black, and bold italic

Subheads:	8.5 pt
Text:	8.5 pt
Text Leading:	9.25 pt
Bullets:	8.5 pt
Hairlines:	.5 pt

Avg Horizontal Scale: 80% Avg Kerning: 0

SCALE 100%

BACK

PACKAGE INSERT

Warnings

Do not use if you know you are allergic to lovastatin

Stop using and tell your doctor right away if you develop new or unusual muscle pain, tenderness or weakness that you can't explain (especially if you have a fever or feel ill). This is because on rare occasions, muscle problems can be serious, including muscle breakdown resulting in kidney damage. This side effect can occur even if you have been on MEVACOR™ Daily for a long period of time.

Ask a doctor before use if you

- are taking prescription cholesterol medicines. Do not substitute. This product is probably not strong enough for you
- have LDL "bad" cholesterol 171 to 400. You are at higher risk for heart disease
- are a woman under age 55 or a man under age 45. You may be at lower risk for heart disease
- are a woman with high HDL "good" cholesterol 60 to 200. You may be at lower risk for heart disease
- have liver disease
- have had heart disease
- have had a stroke
- have diabetes

Ask a doctor or pharmacist before use if you are

- unsure of your cholesterol numbers or have not had a fasting cholesterol test within the last year
- taking any of the following **(because certain drugs or foods can cause interactions and may increase the risk of muscle side effects):**
  - cholesterol medicines
  - oral antibiotics
  - oral antifungals
  - drugs for irregular heartbeat
  - HIV protease inhibitors
  - cyclosporine (immune suppressant)
  - nefazodone (antidepressant)
  - large quantities of grapefruit juice (more than 1 quart daily)

When using this product, talk to a doctor if there is a change in your health, such as a new prescription medicine or a new medical condition.

If pregnant or breast-feeding, or think you may become pregnant, do not use. This product may cause problems in the unborn child.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- this product is only for you if
  - you are a woman 55 years or older or a man 45 years or older and
  - your LDL "bad" cholesterol is between 130 and 170 and
  - you also have one or more of the following heart disease factors which increase your chance of a heart attack:
    - high blood pressure or taking medicine to control your blood pressure or
    - family history of heart disease: father or brother before age 55, mother or sister before age 65 or
    - smoker (smoking increases your risk) or
    - low HDL "good" cholesterol 1 to 39
- take only one tablet daily with your evening meal (your body makes more cholesterol at night)
- continue to eat a healthy diet and exercise
- after 6 weeks get a fasting cholesterol test to see if your LDL "bad" cholesterol has reached a healthy level:
  - LDL "bad" cholesterol 1 to 129. It's working, keep taking it daily and test your cholesterol once a year
  - LDL "bad" cholesterol 130 to 400. This product may not be strong enough for you. Talk to a doctor about using a prescription cholesterol medicine
- if you stop taking this product, your cholesterol will go back up

Other information

- before using this product, you must have tried a healthy diet and exercise to reduce your cholesterol
- before using this product, read the materials enclosed in this package for additional important information
- store at 5°-30° C (41°-86° F)

Inactive ingredients Butylated hydroxyanisole (BHA), cellulose, FD&C blue No. 2 aluminum lake, lactose, magnesium stearate, and starch

Questions? Call toll-free 1-800-_____ from __a.m. to __p.m. (ET) Monday to Friday or visit our website anytime at www.xxxxxxx.com

8¼"

6¾"

Labeling Format Information:

Fonts: Helvetica roman, bold, black, and bold italic

Heads:	10.5 pt	**Bullets**:	8.5 pt
Subheads:	8.5 pt	**Hairlines**:	.5 pt
Text:	8.5 pt		
Text Leading:	9.25 pt		

Avg Horizontal Scale: 80% Avg Kerning: 0

SCALE 100%

SOCIAL SCIENCE REVIEW

Food and Drugs Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products

NDA: 21-213
Type of Submission: Pivotal SELECT Label Comprehension Study #087
Muscle Warning Study #088
Product/Ingredient Name: Mevacor Daily (lovastatin 20 mg)
Dosage Form Route of Administration: oral
Sponsor: Merck Research Laboratories
Date Submitted: July 26, 2007
Date Received: August 2, 2007
Date Review Completed: October 11, 2007
Reviewer: Laura Shay, RN, MS, C-ANP, Social Science Analyst

Introduction
This document is a review of the Pivotal SELECT Label Comprehension Study #087 and the Muscle Warning Comprehension Study #088 conducted in support of NDA 21-213.

Background
On December 10, 1999, Merck Research Laboratories (MRL) submitted a New Drug Application (NDA) for 10 mg nonprescription lovastatin for the treatment of elevated cholesterol for primary prevention of coronary heart disease. On October 6, 2000, MRL was issued a Not Approvable action letter. On August 24, 2004 MRL submitted a complete response to the Not Approvable action letter. The August 24, 2004 resubmission addressed the deficiencies cited in the October 6, 2000 letter and provided new data to support an increased dose (20 mg). On February 23, 2005, MRL was issued a Not Approvable action letter. One of the deficiencies cited in the February 23, 2005 letter was the need to modify and retest the package label. This deficiency was based on the results from the pivotal label comprehension and actual use studies which demonstrated low comprehension rates for a number of communication objectives including the pregnancy warning, the muscle warning, medical conditions that require consultation with a health care professional prior to use and those conditions which preclude use. On July 26, 2007, MRL submitted a complete response to the February 23, 2005, Not Approvable letter. This resubmission contains results from the Self Evaluation of Lovastatin to Enhance Cholesterol Treatment (SELECT) Study #086, the Pivotal SELECT Label Comprehension Study #087, and the Muscle Warning Comprehension Study #088. The following is the review of Study #087 and #088. A separate review was preformed on study #086 by the Medical officer in the Division of Nonprescription Clinical Evaluation.

General Comment:
The exclusion criteria for both the Pivotal SELECT Label Comprehension Study (#087) and the Muscle Warning Study (#088) only precluded someone from participating if he/she had participated in a market research survey in the mall in the past 3 months. It did not preclude anyone from participating if they had participated in previous label comprehension studies (including the Pre-SELECT Label Comprehension) or actual use studies for Mevacor. If someone had participated in another Mevacor study, their responses are potentially biased due to learning that may have occurred from participating in previous studies. MRL was sent a request to provide

data on subjects who participated in more than one study. MRL was able to conduct an analysis based on age, initials, gender and birth in order to identify matches across the following studies: Pre-SELECT label comprehension study, Pivotal SELECT Label Comprehension Study, SELECT self-selection study, and the CUSTOM (Consumer Use of OTC Mevacor) Actual Use Study. The overlap was presented in the following table:

Number of Potential Duplicates per Study Comparisons

	#086 SELECT	Pre-SELECT Label Comp	#087 Pivotal Label Comp	#088 Muscle Comp
#084 CUSTOM	31	3	3	2
#086 SELECT		8	0	2
Pre-SELECT Label Comp			10	3
#087 Pivotal Label Comp				2

This table indicates minimal overlap occurred in the label comprehension studies (Pre-SELECT Label Comprehension, Pivotal SELECT Label Comprehension, and Muscle Warning Label Comprehension), with the largest overlap (n=10) occurring with the Pre-SELECT Label Comprehension Study and the Pivotal SELECT Label Comprehension. Ideally, these 10 subjects should be removed and the data reanalyzed, however it is unlikely that removing these ten subjects would change the outcome of the study.

Reviews

I. Study Title: Pivotal SELECT Label Comprehension Study #087

Purpose:
To test comprehension of two labels: LDL-Cholesterol (LDL-C) label and Total-Cholesterol (Total-C) label (see Attached) in both the general representative sample of adults and low literate adults.

Study Background:
According to MRL, the Pre- SELECT Label Comprehension Study was fielded in October 2006. The primary goal of the Pre-SELECT Label Comprehension Study was to choose the strongest LDL-Cholesterol (LDL-C) label and Total-Cholesterol (Total-C) label to be used in the Pivotal SELECT Label Comprehension Study #087 and the SELECT Self-Selection study #086. Pre-SELECT Label Comprehension Study was a five-cell study conducted in 25 geographically and demographically dispersed malls. Sample size was approximately 150. Subjects were randomized to one of five different versions of the label. The total sample was augmented with 100 women between the ages of 18 and 54 in order to confirm that women understood the key label messages directed to women (appropriate age and not to use if pregnant, plan to become pregnant or breastfeeding). The study questionnaire consisted primarily of scenario based questions describing hypothetical individuals. Based on the scenario, participants were asked if it was “ok” or “not ok” for the hypothetical individual to start to use or continue to use Mevacor™ Daily followed by a

question that asked why the participants gave their response. According to MRL, all of the absolute safety warnings scored a comprehension rate of 97% or higher for all five of the labels and the flow design versus the chart design for the LDL and cholesterol information achieved higher scores.

In December 2006, MRL conducted the Pivotal SELECT Label Comprehension Study (study # 087). The LDL-Cholesterol (LDL-C) label with non-Drug Facts flow chart and the Total-Cholesterol (Total-C) label non-Drug Facts flow chart were the labels tested (see Appendix 1). The questionnaire used was the same as the one used in the pilot study (Pre-SELECT Label Comprehension Study).

According to MRL the package labels used in the SELECT self-selection Study (#086) were nearly identical to those tested in the Pivotal SELECT Label Comprehension Study. Only two minor changes were made to improve clarity:

1. The words "lower" and "higher" were bolded in the flow charts of both labels within the text next to the LDL-C or Total-C box
2. The last box on the flow chart of the Total-C label was modified to be consistent with the text on the LDL-C label.

Reviewer's Comment
It is important to note that the labels tested in the Pre-Select Label Comprehension Study and the Pivotal Label Comprehension Study were significantly different than the label used in the actual use study (Consumer Use of OTC Mevacor-CUSTOM study). See Appendix 2. No comparison was made in this current study.

Objectives:

Primary objective: To measure consumer comprehension of the following communication messages on the label:

- What the product is and what it is used for
- Criteria for use (diet and exercise, cholesterol numbers from fasting test, age/gender)
- Warnings and cautions (Do not use, Ask a doctor before use, Ask a doctor or pharmacist before use)
- When using product: what to do if change in health or unexplained muscle pain
- Directions for use (who could use, dose, goal messages)

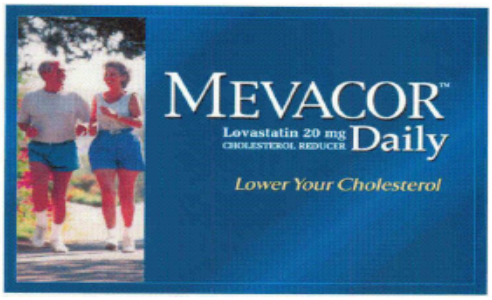
Secondary objective: To test comprehension of two different usage paradigms based on LDL-C and Total-C

Study Design:
The study was a parallel two group design, with respondents randomized to evaluate and answer comprehension questions based on either the (1) nonprescription lovastatin package labeling based on lowering LDL-C or the (2) nonprescription lovastatin package label based on lowering Total-C.

Recruitment/Screening: Potential respondents were approached on the mall floor and administered a screener questionnaire and asked their level of cholesterol concern. Respondents who met the eligibility criteria and were either extremely or very concerned about their cholesterol were then shown a brief description of Mevacor™ Daily (see Figure 1 submitted by MRL). Those who indicated that they would either definitely, probably or might consider using Mevcor™ Daily were enrolled into the study.

Figure 1: Recruitment Material

Introducing New Non- Prescription Mevacor™ Daily



The Simple Way to Lower Your Cholesterol!

Nowadays, most of us realize that one of the best ways to reduce the risk of heart disease is to lower our cholesterol. And that's why Mevacor™ Daily was created.

New non-prescription Mevacor™ Daily has been clinically proven to lower cholesterol, which can significantly reduce your risk of heart disease. Mevacor™ Daily is a tiny tablet, so it is easy to take. And because Mevacor™ Daily was previously sold only by prescription, it's been proven safe and effective for nearly 20 years.

Inclusion Criteria:

- Age 18 or older
- Must be extremely or very concerned about cholesterol (on a 4 point scale of extremely, very, somewhat and not at all concerned)
- Must say definitely, probably, or might-might not consider using Mevacor ™ Daily (on a 4 point scale of definitely, probably, might-might not, definitely would not consider using)
- For low literacy respondents: Mispronounces or fails to pronounce six or more words on the REALM test (corresponding to an 8th grade reading level or below)

Exclusion Criteria:

- Participation in a market research survey in the mall in the past 3 months
- Employment of respondent, family or close friends in the following areas
    - By an advertising agency
    - By a market research company
    - By a company that processes or manufactures pharmaceutical, medical, or healthcare products
    - As a physician, nurse or pharmacist
- Reading glasses needed but not available

Reviewer's Comment

As stated in the background information, the exclusion criteria for this study only precluded someone from participating if he/she had participated in a market research survey in the mall in the past 3 months. It did not preclude anyone from participating if they have participated in previous label comprehension studies (including the Pre-SELECT Label Comprehension) or actual use studies for Mevacor. If someone had participated in another Mevacor study, their responses are potentially biased due to learning that may have occurred from participating in previous studies. It appears that ten subjects participated in both the Pre-SELECT Label Comprehension Study and the Pivotal SELECT Label Comprehension. Ideally, these 10 subjects

should be removed and the data reanalyzed, however it is unlikely that removing these ten subjects would change the outcome of the study.

Study Sites:
The study was conducted in 20 geographically and demographically dispersed malls across the country. Figure 2 is a list of the study locations.

Figure 2: Study Locations

01( ) Boston, MA	06( ) Cleveland, OH	11( ) New York, NY	16( ) San Antonio, TX
02( ) Bridgeport, CT	07( ) Colorado Springs, CO	12( ) Philadelphia, PA	17( ) San Francisco, CA
03( ) Buffalo, NY	08( ) Houston, TX	13( ) Phoenix, AZ	18( ) Seattle, WA
04( ) Chicago, IL	09( ) Indianapolis, IN	14( ) Portland, OR	19( ) Springfield, MO
05( ) Cincinnati, OH	10( ) Los Angeles, CA	15( ) Raleigh-Durham, NC	20( ) Tampa, FL

Sample:
Sample size determination was based on a 90% and 95% confidence interval around the point estimate of 50%. The resulting value equated to a sample size of 300 representative respondents in each group and 150 low literacy respondents in each of the low literacy groups.

Reviewer's Comments
It is unclear why the sample size determination was based on both a 90% and a 95% confidence interval around the point estimate of 50%, however the sample size appears to be adequate.

The total representative respondents in each group include both normal literate and low literate participants. The low literacy groups includes the low literate respondents from the total representative group plus low literate respondents recruited specifically to augment the total number of low literacy respondents.

In order to ensure that the sample would be representative of the broader population from an age and gender perspective, age and gender quotas were set to ensure equal distribution in each group.

Data collection method:
Data was collected through interviews. Study questions asked by the interviewer were in scenario format describing hypothetical individuals. Each scenario was typically asked in two parts: first the respondent was asked if it was "ok" or "not ok" for the hypothetical person to use or to continue to use Mevacor™ Daily, followed by an open-ended question asking the respondent why they gave the response they did. The open-ended responses were captured verbatim. False positive scenarios were also used to test whether respondents could make appropriate assessments of situations not specifically addressed on the label.

Coding categories for each of the open-ended responses were pre-determined based on the Pre-SELECT Label Comprehension Study. MRL states that coding rules were developed to classify the responses as either "correct", "acceptable" or "incorrect" based on the label information. Coding was performed by Bruno and Ridgway Research Associates Inc. Their coding process is described as follows: Coding was based on at least 50% of the verbatim responses. The codes were grouped by response category and placed into a code book. The coder read through every answer and coded the responses. The codebook was updated with new coding responses. Answers that did not fit into any of the codes in the codebook were listed in the miscellaneous list. A second coder checked the codes assigned to every answer. All discrepancies were discussed among the coders and project manager.

MRL describes that the only difference between the questionnaires in each of the groups was those questions that referred to LDL-C or Total-C.

Reviewer's Comments

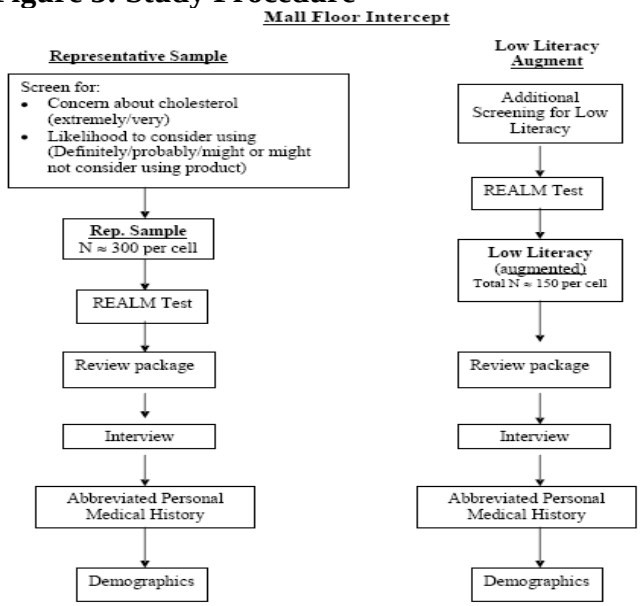
The questionnaire and recruitment material do not appear to pose any bias. All questions that required an "ok", "not ok", "don't know", "correct" or "incorrect" response were followed by an open-ended question asking the respondent why he/she said what they said. The standard coding process was employed without noted bias.

Study Plan:

Eligible respondents were told that the interview would take approximately 45 minutes and that they would be compensated with $20 to participate. Participants who did not have enough time to participate at the time of screening were asked to return. Those participants were given an additional $5 for travel expenses. All participants were asked to sign a non-disclosure form. The Rapid Estimate of Adult Literacy (REALM) was used to determine the reading level of each Respondent. Respondents who missed 6 or more words (corresponding to an 8th grade reading level or lower) were classified as low literate.

Participants were provided with either the LDL-C product label or the Total-C product label to review, followed by the interview. Participants were able to refer to the product label during the interview. The study procedure is represented in Figure 3, provided by the MRL:

Figure 3: Study Procedure



Data Analysis:

The primary analysis was conducted on the percent of respondents in the representative sample who gave "correct", "acceptable", and "incorrect" responses.

Low Literacy subgroup (the low literacy subjects within the representative sample plus the augmented low literacy respondents) was compared with the total representative sample.

Analysis by gender was performed on four questions that apply specifically to women (pregnancy, breast feeding and high HDL).

Results:

Demographic Data:
Table 1, submitted by MRL, summarizes the demographics of the total sample and the augmented low literate sample:

Table 1: Demographics

Demographics of Representative and Low Literacy Respondents

	Total Representative Sample		Total Low Literacy Sample*	
Sample Size	N=610		N=315	
	N	%	N	%
Gender				
Male	277	45	176	56
Female	333	55	139	44
Age				
18-34	154	25	123	39
35-44	130	21	64	20
45-54	122	20	56	18
55+	204	33	72	23
Race				
Caucasian	463	76	197	63
Non-Caucasian	149	24	120	38
African-American	71	12	58	18
Hispanic	71	12	52	17
Asian/Pacific	11	2	8	3
Amer. Indian/ Alaskan Native	1	<1	4	1
Other	3	<1	0	0
Education				
HS incomplete or less	54	9	69	22
HS graduate	224	37	150	48
College	289	47	90	29
Some college	115	19	44	14
Degree/vocational	174	29	46	15
Post-college	36	6	4	1
Unspecified	7	1	2	1

*Includes augmented respondents.

Table 2, composed from the data submitted, shows sample size for each study group

Table 2: Sample Size for Each Study Group

Representative Sample		Low literacy Sample	
N=610		N=315	
LDL-C	Total-C	LDL-C	Total-C
307	303	155	160

Table 3, composed from the demographic dataset submitted by MRL, shows male and female participants broken down by age range.

Table 3: Distribution of Subjects by Age

Age	Total n=816	
	Female (n=422)	Male (n=394)
18-25	59 (14%)	76 (19%)
26-35	60 (14%)	62 (16%)
36-45	85 (20%)	82 (21%)
46-55	78 (18.4%)	81(20%)
56-65	76 (18%)	55 (14%)
66-75	34 (8%)	21 (5%)
76-85	14 (3%)	6 (1%)
>86	1 (0.2%)	1 (0.2%)
Refused	15	10

Reviewer's Comments:
The demographic make up of the 2 label paradigm groups are comparable.
An adequate number of respondents were tested in all age groups. Greater than 50% of the females were under the age of 55.

Results from the Interview Questions

MRL submitted tables with the results of all the study questions for the combined label groups and each of the label groups independently (LDL-C and HDL-C). These tables are divided into the "Correct" and "Incorrect" responses to the questions dealing with the use and directions for use of the product (Table 7), the "Ok" "Not okay", and "I don't know" responses to the scenario questions (Table 8), and the "Correct "and "Acceptable" responses to the scenario questions based on analysis ("gestalt analysis") of the verbatim answers to the open-ended questions (Table 9).

MRL presented the results from the correct answers and the results from the "gestalt" correct answers in separate tables. For the purposes of this review, all of the correct and "gestalt" correct answers are presented together in Tables 5-15 below. The order the questions are listed is based on clinical significance (e.g. questions pertaining to the absolute contraindications on label will be presented first). The following is a description of the key elements contained in Tables 4-14:

The number of participants who correctly answered the closed-ended question (ok, not ok, I don't know or correct, incorrect)

Two Label Paradigms

	LDL-C				Total-C			
	Rep N=307		Low Lit N=155		Rep N=303		Low Lit N=160	
	N	%	N	%	N	%	N	%
Question –Correct	290	94	140	90	280	92	143	89
Gestalt Analysis: Correct	281	92	137	88	279	92	141	88
Gestalt Analysis: Acceptable	4	1	1	1	4	1	2	1
Gestalt Analysis: Correct+Acceptable	285	93	138	89	283	93	143	89

The number of participants whose answer remained correct after the open-ended question "why did you say that" was analyzed.

The number of participants who answered the closed-ended question incorrectly but provided an open-ended response that was considered acceptable

The combined number of participants who provided either a correct or an acceptable answer based on the analysis of the open-ended question.

MRL describes the following coding rules for responses that were not "clear-cut":

1. A participant's answer was considered <u>acceptable</u> if they provided the incorrect answer "not ok to use" for questions that asked about hypothetical situations not listed on the label and their response to the open-ended question was that the person should "talk to their doctor."
2. For questions that reference a portion of the label that directs the consumer to ask a doctor, a participant's answer was considered <u>acceptable</u> if they provided the correct answer "not

ok to use" but their response to the open-ended question was "okay to use if they talk to their doctor."

3. For questions that reference a portion of the label that does not direct the consumer to ask a doctor, a participant's answer was considered <u>incorrect</u> if they provided the correct answer "not ok to use" but their response to the open-ended question was "okay to use if they talk to their doctor."

<u>Reviewer's Comments</u>
The coding rules for responses that were not "clear cut" were provided by MRL in Table 6 of their submission. As presented, the table was not clear. A T-con was requested with MRL to provide clarification. The T-con took place on August 20, 2007. The summary provided above is based on that discussion.

Overall, based on the analysis of the open-ended questions, the percentage of gestalt correct answers were either the same as the percentage of correct answers or lower than the percentage of correct answers. Therefore, it is clear that some of the participants may have guessed correctly but when asked why they answered the way they did, they could not explain.

There were few cases in which the gestalt correct answers were slightly higher than the correct answer. MRL described that on a rare occasion, no response was recorded to the correct-incorrect answer or the ok, not ok, I don't know answer but there was a response recorded to the open-ended question. In these cases when the respondent answered the open-ended answer correctly, the percentage of total correct gestalt answers ended up being slightly higher than the percentage of total correct answers.

Table 4: Absolute Contraindications: Allergy, Pregnant, Breast Feeding

	LDL-C				Total-C			
	Rep N=307		Low Lit N=155		Rep N=303		Low Lit N=160	
	N	%	N	%	N	%	N	%
Q22 Allergic to lovastatin-Correct	304	99	141	91	295	97	148	93
Gestalt Analysis: Correct	304	99	141	91	296	98	148	93
Gestalt Analysis: Acceptable	0	0	0	0	0	0	0	0
Gestalt Analysis: Correct+Acceptable	304	99	141	91	296	98	148	93
Q7 Pregnant-Correct	301	98	151	97	296	98	155	97
Gestalt Analysis: Correct	300	98	146	94	296	98	155	97
Gestalt Analysis: Acceptable	0	0	4	3	1	<1	0	0
Gestalt Analysis: Correct+Acceptable	300	98	150	97	297	98	155	97
Q30 Breast Feeding-Correct	299	97	153	99	293	97	154	96
Gestalt Analysis: Correct	297	97	151	97	287	95	151	94
Gestalt Analysis: Acceptable	0	0	1	1	2	1	1	1
Gestalt Analysis: Correct+Acceptable	297	97	152	98	289	95	152	95

MLR submitted the following table constructed from responses to the pregnancy question. The table consists of combined results from both labels separated by gender and women who were less than age 55:

Pregnant (Alice, Q7)
Do Not Use

	TOTAL MEN N=277		TOTAL WOMEN N=333		WOMEN < 55 N=214	
COMBINED CELLS	N	%	N	%	N	%
GROUP SAMPLE SIZES:		A		B		
Correct/Acceptable	270	97	327	98	209	98
Correct	270	97	326	98	208	97
Acceptable	0	0	1	<1	1	<1
Incorrect	7	3	6	2	5	2

<u>Reviewer's Comments</u>
The percentage range for gestalt correct responses (correct responses based on validation from the open-ended question) for the absolute contraindications to lovastatin (allergy to lovastatin, pregnancy, breast feeding) was 91-99%. The lower percentage rate occurred in the low-literate populations.

The range of gestalt correct responses to the pregnancy and breast feeding questions were 94-98%. The total number of women under the age of 55 was 214. Results indicate that 6 out of 333 women (2%) answered the pregnancy question incorrectly, most of whom (five out of the six) were under the age of 55.

Four respondents in the LDL-C low literate populations and one respondent from the Total-C representative populations provided open-ended answers for the pregnancy question that MRL considered "acceptable". These "acceptable" answers were:

1. *"she has to be older to take this medicine"*
2. *"for older adults"*
3. *"you have to be age 55"*
4. *"she is not the right age"*
5. *"she is under 55"*
6. *"for older adults"*

All of these "acceptable answers" had to do with incorrect age and not pregnancy, therefore they should not have been considered acceptable. MRL also considered answers to the breastfeeding question "acceptable" if the respondent stated the reason was due to her age. Those responses should also not be considered acceptable.

Open ended responses from all 13 of the respondents who answered the pregnancy question incorrectly were primarily due to not being able to find the pregnancy warning on the package. The following is a list of the verbatim statements that refer to the inability to find the pregnancy information:

1. *"Because it does not say do not take if you are pregnant"*
2. *"I don't see anywhere on the package where it says she can't"*
3. *"I don't see anything if you are pregnant"*
4. *"The label doesn't say anything about pregnancy"*
5. *"It doesn't have any restrictions"*
6. *"It should be ok, the box doesn't specify"*
7. *"It doesn't say anything about pregnancy"*
8. *"Doesn't say anything about pregnancy"*
9. *"I don't see that any place to answer"*
10. *"Because what I read on the box did not say anything about pregnancy at all so she is not at risk"*
11. *"Cause on the thing it does not break down pregnancy"*

Open ended responses from the respondents who answered the breast feeding question incorrectly were also primarily based on not being able to find the pregnant-breastfeeding warning on the package. Additionally, some respondents stated that it is ok for a woman to take Mevacor™ Daily as long as she is not pregnant. It appears from these responses that the message "may become pregnant" was not taken into consideration. The concept "may become pregnant" was not independently tested, therefore the ability to comprehend this concept is unknown.

Table 5: When to Stop Taking Mevacor™ Daily and Talk to a Doctor

	LDL-C				Total-C			
	Rep N=307		Low Lit N=155		Rep N=303		Low Lit N=160	
	N	%	N	%	N	%	N	%
Q36 Unexplained Muscle Pain-Correct	300	98	149	96	293	97	154	96
Gestalt Analysis: Correct	300	98	149	96	293	97	154	96
Gestalt Analysis: Acceptable	0	0	0	0	0	0	0	0
Gestalt Analysis: Correct+Acceptable	300	98	149	96	293	97	154	96

Reviewer's Comments
The range of gestalt correct responses to the question asking if someone should continue using Mevacor™ Daily if they have unexplained muscle pain was high (96-98%).

Table 6: Indication, Active Ingredient, Dosing

	LDL-C				Total-C			
	Rep N=307		Low Lit N=155		Rep N=303		Low Lit N=160	
	N	%	N	%	N	%	N	%
Q2b Indication-Correct	303	99	149	96	301	99	155	97
Q2c Active Ingredient-Correct	281	92	121	78	273	90	129	81
Q9a Number of times per day-Correct	296	96	144	93	295	97	148	93
Q9b Number of tablets at once-Correct	295	96	141	91	293	97	151	94
Q20a Is There Best time of day-Correct	275	90	126	81	272	90	135	84
Q20b- Best Time of Day-Correct	256	83	111	72	243	80	110	69

Reviewer's Comments
The range of correct responses to the indication question was high (96-97%). The range of correct responses to the active ingredient question was low for the low literate populations (78-81%) and was not much higher for the total representative populations (90-92%). Some respondents stated the inactive ingredient. Placement of the active ingredient information on both labels is on the outer flap separate from the rest of the Drug Facts label. This may have contributed to the low scores.

The overall range of correct responses to the questions addressing the number of tablets to take at one time and the number of tablets to take per day were adequate (91-96%). Ten respondents in the total representative populations for both labels (n=610) stated that two tablets should be taken at one time (four of the ten respondents were from the low literate population). Eight respondents in the total representative populations for both labels (n=610) stated that Mevacor™ Daily should be taken two times a day (three of the eight respondents were from the low literate population). One low-literate respondent stated that three doses of Mevacor™ Daily should be taken three times a day (daily dose of 180 mg) . Two respondents (one from one of the representative populations and one from the low literate population) stated a total daily dose of 80 milligrams (two 20 mg doses two times).

The overall range of correct responses to the questions addressing the best time of day to take Mevacor™ Daily was also low (69-83%). The concept of an "evening meal" may be difficult to comprehend. Results may have been higher if the label used statements more commonly found on medication labels e.g. "take at dinner time" or "take at bedtime".

Table 7: Decision based on Age

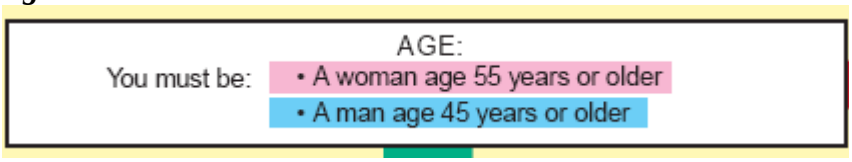
	LDL-C				Total-C			
	Rep N=307		Low Lit N=155		Rep N=303		Low Lit N=160	
	N	%	N	%	N	%	N	%
Q24 Female <55-Correct	290	94	140	90	280	92	143	89
Gestalt Analysis: Correct	281	92	137	88	279	92	141	88
Gestalt Analysis: Acceptable	4	1	1	1	4	1	2	1
Gestalt Analysis: Correct+Acceptable	285	93	138	89	283	93	143	89
Q27 Female >55-Correct	277	90	140	90	271	89	140	88
Gestalt Analysis: Correct	258	84	132	85	259	85	137	86
Gestalt Analysis: Acceptable	13	4	3	2	10	3	3	2
Gestalt Analysis: Correct+Acceptable	271	88	135	87	269	89	140	88
Q34 Male <45-Correct	291	95	143	92	282	93	139	87
Gestalt Analysis: Correct	280	91	141	91	276	91	137	86
Gestalt Analysis: Acceptable	9	3	3	2	9	3	3	2
Gestalt Analysis: Correct+Acceptable	289	94	144	93	285	94	140	88

Reviewer's Comments

The range of gestalt correct responses to the age based questions was 84-92%. There was little difference between label paradigms or between the total representative populations and the low literate populations. Given that the tested labels have a pink highlight over the statement "A women age 55 years or older" and a blue highlight over the statement "A man age 45 years or older", it surprising that the level of comprehension was not higher. This highlighting is located on the Principal Display Panel and on the flow chart outside of the Drug Facts Label. The age statements are not highlighted in the Drug Facts Label (see figures below). It is important to note that the age statements located outside of Drug Facts are written as absolute contraindications (e.g., "This Product is only for", and "You Must be"). Whereas the age statement located in the Drug Facts label is under the subheading "Ask a doctor before use if you" which is not an absolute contraindication. Because age is not listed as an absolute contraindication in the Drug Facts label, a number of responses were considered "acceptable" if they stated that the individual who was not within the correct age range needed to talk to their doctor. The addition of the "acceptable" answers to the correct answers increased the range of correct answers to 87-94%.

Age Statement on Principal Display Panel

Age Statement on Flow Chart



Age Statement in Drug Facts

Warnings

Do not use if you know you are allergic to lovastatin

Ask a doctor before use if you

- are taking prescription cholesterol medicines. Do not substitute. This product is probably not strong enough for you
- have LDL "bad" cholesterol 171 to 400. You are at higher risk for heart disease
- are a woman under age 55 or a man under age 45. You may be at lower risk for heart disease
- are a woman with high HDL "good" cholesterol 60 to 200. You may be at lower risk for heart disease
- have liver disease
- have had heart disease
- have had a stroke
- have diabetes

Sixteen out of 333 women (5%) answered the question related to the under age female scenario incorrectly and 9 out of 214 (4%) women less than age 55 answered the question incorrectly. See table below submitted by MRL.

38-Year-Old Woman (Laurie, Q24)
Talk to Doctor First

	TOTAL MEN N=277		TOTAL WOMEN N=333		WOMEN < 55 N=214	
COMBINED CELLS GROUP SAMPLE SIZES:	N	% A	N	% B	N	%
Correct/Acceptable	259	94	309	93	202	94
Correct	255	92	305	92	200	93
Acceptable	4	1	4	1	2	1
Incorrect	15	5	16	5	9	4
Elevated cholesterol	4	1	6	2	2	1
Not Classified	3	1	7	2	2	1
Unspecified	0	0	1	<1	1	<1

Statistical differences are tested in columns A vs. B. Capital letters indicate differences at the 95% confidence level and small letters indicate differences at the 90% confidence level.

Table 8: Decisions Based on Risk Factors/LDL/HDL/Total-C

	LDL-C				Total-C			
	Rep N=307		Low Lit N=155		Rep N=303		Low Lit N=160	
	N	%	N	%	N	%	N	%
Q6 Doesn't know numbers-Correct	299	97	142	92	289	95	148	93
Gestalt Analysis: Correct	299	97	140	90	289	95	147	92
Gestalt Analysis: Acceptable	4	1	4	3	4	1	3	2
Gestalt Analysis: Correct+Acceptable	303	99	144	93	293	97	150	94
Q11 LDL-C/Total-C in range-Correct	229	75	116	75*	259	85	133	83*
Gestalt Analysis: Correct	225	73	112	72*	253	83	131	82*
Gestalt Analysis: Acceptable	1	<1	3	2	3	1	1	1
Gestalt Analysis: Correct+Acceptable	226	74	115	74	256	84	132	83
Q15 High HDL-Correct	239	78	119	77	247	82	132	83
Gestalt Analysis: Correct	196	64*	101	65	226	75*	117	73
Gestalt Analysis: Acceptable	6	2	3	2	5	2	3	2
Gestalt Analysis: Correct+Acceptable	202	66*	104	67	231	76*	120	75
Q17 High LDL-C/Total-C-Correct	218	71	101	65	221	73	110	69
Gestalt Analysis: Correct	211	69	99	64	217	72	112	70
Gestalt Analysis: Acceptable	9	3	4	3	10	3	5	3
Gestalt Analysis: Correct+Acceptable	220	72	103	66	227	75	117	73
Q31 Low LDL-C/Total-C -Correct	249	81*	122	79	264	87*	130	81
Gestalt Analysis: Correct	240	78*	115	74	260	86*	125	78
Gestalt Analysis: Acceptable	0	0	0	0	4	1	0	0
Gestalt Analysis: Correct+Acceptable	240	78*	115	74	264	87*	125	78
Q14 Diet/Exercise-High LDL -Correct	245	80*	120	77	266	88*	134	84
Gestalt Analysis: Correct	236	77*	113	73	262	86*	133	83
Gestalt Analysis: Acceptable	7	2	6	4	3	1	0	0
Gestalt Analysis: Correct+Acceptable	243	79*	119	77	265	87*	133	
Q8 Presence of MI risk factor-Correct	143	47	60	39	139	46	49	31
Gestalt Analysis: Correct	134	44	53	34	131	43	46	29
Gestalt Analysis: Acceptable	7	2	5	3	3	1	1	1
Gestalt Analysis: Correct+Acceptable	141	46	58	37	134	44	47	29

*****Statistical Difference at 95% CI

Reviewer's Comments

Most respondents understood that a person needs to know their cholesterol numbers before he/she uses Mevacor™ Daily (range of gestalt correct responses 90-97%). However, many of the respondents did not understand how to make decisions on whether or not to use Mevacor™ daily based on the cholesterol results or one of the risk factors (having a mother who had a heart attack at age 50). The range of gestalt correct responses was 29-86%. The range of gestalt correct responses for the representative populations was 44-86% and the range of gestalt correct responses for low literate populations was 29-83%. The Total-C label tested better than the

LDL-C label on questions related to cholesterol numbers (70-86% versus 64-78%). The risk factor question had the lowest range of gestalt correct responses for both labels (29-44%).

Table 9: Cholesterol Testing

	LDL-C				Total-C			
	Rep N=307		Low Lit N=155		Rep N=303		Low Lit N=160	
	N	%	N	%	N	%	N	%
Q13 Timing of testing before use-Correct	264	86	112	72	272	90	126	79
Gestalt Analysis: Correct	260	85	104	67	269	89	121	76
Gestalt Analysis: Acceptable	4	1	3	2	2	1	2	1
Gestalt Analysis: Correct+Acceptable	264	86	107	69	271	89	123	77
Q16-Fasting before test -Correct	276	90	123	79	283	93	141	88
Gestalt Analysis: Correct	271	88	122	79	266	88	129	81
Gestalt Analysis: Acceptable	3	1	2	1	7	2	3	2
Gestalt Analysis: Correct+Acceptable	274	89	124	80	273	90	132	83
Q38a Need for retesting -Correct	265	86	120	77	256	84	127	79
Q38b When to retest-Correct	189	62	72	46	186	61	72	45

Reviewer's Comments

The low literate populations had difficulty understanding that cholesterol testing should be performed prior to starting Mevacor ™ Daily (range of gestalt correct responses 67-76%). The range of gestalt correct response from the representative populations was higher (86-90%). Understanding the need to fast prior to testing was slightly higher for the low literate populations (79-81%) than the understanding of cholesterol testing prior to use (67-76%).

The statement that instructs consumers to base their decision to use Mevacor ™ Daily on a fasting cholesterol test that has been performed in the past year is stated the following ways: "Your LDL "Bad" cholesterol is between 130-170 based on a fasting cholesterol test within the past year" (LDL-C label) or "Men and women must have a total cholesterol between 200-240 based on a fasting cholesterol test within the past year" (Total-C label). The wording "on a fasting cholesterol test within the past year" may be confusing because it leaves out the words "that has been done". This may have contributed to the low number of correct responses.

The range of correct gestalt answers for the need to retest cholesterol levels and when to retest cholesterol questions were low (45-86%) with the lower number of correct responses found in the low literate populations (45-77%). More participants understood the need to retest (77-86%) than understood when to retest (45-62%). The cholesterol retesting messages on the current label are subtle: "after 6 weeks get a fasting cholesterol to see if your LDL "bad" cholesterol has reached a healthy level"(LDL-C label) or "after 6 weeks get a fasting cholesterol test to see if your total cholesterol has reached a healthy level" (Total-C label). Because it is important for someone to be sure they are receiving an adequate dose of medication, the statement on the label needs to be stronger and possibly enhanced (e.g. You Must Recheck Your Fasting Cholesterol in 6 Weeks to be Sure the Medicine is Working for You).

Table 10: When to Talk to A Doctor or Pharmacist-Before Taking Mevacor™ Daily

	LDL-C				Total-C			
	Rep N=307		Low Lit N=155		Rep N=303		Low Lit N=160	
	N	%	N	%	N	%	N	%
Q10 Hx Stroke-Correct	274	89	137	88	279	92	146	91
Gestalt Analysis: Correct	268	87**	135	87	278	92**	146	91
Gestalt Analysis: Acceptable	7	2	4	3	5	2	3	2
Gestalt Analysis: Correct+Acceptable	275	90**	139	90	283	93**	149	93
Q12 Hx Liver Disease-Correct	291	95	139	90	289	95	148	93
Gestalt Analysis: Correct	288	94	132	85	287	95	144	90
Gestalt Analysis: Acceptable	9	3	14	9	4	1	8	5
Gestalt Analysis: Correct+Acceptable	297	97	146	94	291	96	152	95
Q26 Hx Diabetes-Correct	288	94	143	92	274	90	147	92
Gestalt Analysis: Correct	289	94**	143	92	273	90**	146	91
Gestalt Analysis: Acceptable	7	2	6	4	11	4	4	3
Gestalt Analysis: Correct+Acceptable	296	96	149	96	284	94	150	94
Q4 On Oral Antibiotic-Correct	275	90	123	79	268	88	131	82
Gestalt Analysis: Correct	269	88	115	74	256	84	121	76
Gestalt Analysis: Acceptable	10	3	8	5	5	2	5	3
Gestalt Analysis: Correct+Acceptable	279	91**	123	79	261	86**	126	79
Q19 On a cholesterol med-Correct	290	94	144	93	286	94	144	90
Gestalt Analysis: Correct	276	90	137	88	271	89	140	88
Gestalt Analysis: Acceptable	6	2	7	5	6	2	6	4
Gestalt Analysis: Correct+Acceptable	282	92	144	93	277	91	146	91
Q25 Grapefruit Juice-Correct	280	91	124	80	272	90	123	77
Gestalt Analysis: Correct	279	91	123	79	269	89	123	77
Gestalt Analysis: Acceptable	6	2	3	2	9	3	2	1
Gestalt Analysis: Correct+Acceptable	285	93	126	81	278	92	125	78
Q32 Rx for fungal infection -Correct	295	96	141	91	283	93	143	89
Gestalt Analysis: Correct	289	94**	136	88	274	90**	139	87
Gestalt Analysis: Acceptable	2	1	6	4	8	3	3	2
Gestalt Analysis: Correct+Acceptable	291	95	142	92	282	93	142	89

** Statistical Difference at 90% CI

Reviewer's Comments

The overall range of gestalt correct responses to the questions addressing when to talk to a doctor or pharmacist before taking Mevacor™ Daily was adequate (87-94%). The exceptions were for the questions that asked if it was ok to use the product if someone is on an antibiotic or if someone drinks large quantities of grapefruit juice. The range of gestalt correct responses to these questions were low for the low literate populations (74-79%) with little improvement when acceptable responses were added (78-81%). The information on the label describing antibiotic use and drinking large quantities of grapefruit juice does not appear any more complex than other

similar statements on the label (e.g., antifungal use and cholesterol medications). Therefore it is unclear why the low literate populations had more difficulty with these questions.

Table 11: When to Talk to a Doctor -When Taking Mevacor™ Daily

	LDL-C				Total-C			
	Rep N=307		Low Lit N=155		Rep N=303		Low Lit N=160	
	N	%	N	%	N	%	N	%
Q37 Developed kidney disease	***Only an Open-Ended Question***							
Gestalt Analysis: Correct	253	82*	114	74	227	75*	115	72
Gestalt Analysis: Acceptable	33	11	35	23	46	15	29	18
Gestalt Analysis: Correct+Acceptable	286	93	149	96	273	90	144	90
Q41 6wks chol. not lower	***Only an Open-Ended Question***							
Gestalt Analysis: Correct	202	66	92	59	208	69	99	62
Gestalt Analysis: Acceptable	5	2	6	4	3	1	3	2
Gestalt Analysis: Correct+Acceptable	207	67	98	63	211	70	102	64

*****Statistical Difference at 95% CI

*Reviewer's Comment***s**

What to do if someone develops kidney disease is not described on the label. The question describing someone who developed kidney disease was designed to see if the respondents understood the statement on the label" "When using this product talk to a doctor if there is any change in your health, such as a new prescription medicine or new medical condition". Based on the range of gestalt correct responses (72-82%), the message may need to be simplified and strengthened (e.g. "When using this product, be sure to talk to your doctor if you have a new medical problem or start taking a new medication").

It is very concerning that the range of gestalt correct responses was so low (59-69%) for the question on what to do if someone's cholesterol is not lower after 6 weeks. There was only a slight improvement when acceptable answers were added (63-70%). As stated above, the messages concerning retesting cholesterol and what to do if someone's cholesterol remains elevated need to be strengthened. If these statements are not strengthened and retested to ensure that they are well understood, many consumers who take Mevacor ™ Daily may not get a benefit from treatment.

Table 12: What Happens When Stop Using Mevacor™ Daily

	LDL-C				Total-C			
	Rep N=307		Low Lit N=155		Rep N=303		Low Lit N=160	
	N	%	N	%	N	%	N	%
Q42 What happens when stop	***Only an Open-Ended Question***							
Gestalt Analysis: Correct	263	86	126	81	253	83	136	85
Gestalt Analysis: Acceptable	22	7	12	8	25	8	8	5
Gestalt Analysis: Correct+Acceptable	285	93	138	89	278	92	144	90

Reviewer's Comments

The number of correct responses to the question regarding what happens when someone stops Mevacor™ Daily was adequate for both the representative populations and low literate populations (81-86%).

Table 13: Change in Eating Pattern Before Taking Mevacor™ Daily

	LDL-C				Total-C			
	Rep N=307		Low Lit N=155		Rep N=303		Low Lit N=160	
	N	%	N	%	N	%	N	%
Q28 Eating Pattern	***Only an Open-Ended Question***							
Gestalt Analysis: Correct	299	97	140	90	289	95	147	92
Gestalt Analysis: Acceptable	4	1	4	3	4	1	3	2
Gestalt Analysis: Correct+Acceptable	303	99	144	93	293	97	150	94

Reviewer's Comments

Although the question is somewhat leading ("Normally Melanie eats foods high in cholesterol. Melanie has decided to use Mevacor™ Daily to lower her cholesterol. What if anything should Melanie do with her eating patterns before she starts to take Mevacor™ Daily?"), most of the respondents understood the need to reduce the amount of cholesterol in the diet before starting Mevacor™ Daily (range of gestalt correct responses 90-97%). Respondents were not tested on behavior modification after starting Mevacor™ Daily.

Table 14: Questions That Did Not Contain Information Found on the Label

	LDL-C				Total-C			
	Rep N=307		Low Lit N=155		Rep N=303		Low Lit N=160	
	N	%	N	%	N	%	N	%
Q5 Problems sleeping-Correct	243	79	111	72	253	83	117	73
Gestalt Analysis: Correct	235	77	106	68	240	79	111	69
Gestalt Analysis: Acceptable	35	11	27	17	36	12	26	16
Gestalt Analysis: Correct+Acceptable	270	88	133	86	276	91	137	86
Q23 Spicy food-Correct	241	79	112	72	248	82	122	76
Gestalt Analysis: Correct	221	72	101	65	228	75	116	73
Gestalt Analysis: Acceptable	50	16	39	25	51	17	30	19
Gestalt Analysis: Correct+Acceptable	271	88	140	90	279	92	146	91
Q33 Tension headaches-Correct	227	74	94	61	219	72	109	68
Gestalt Analysis: Correct	222	72	92	59	212	70	108	68
Gestalt Analysis: Acceptable	41	13	28	16	47	16	26	16
Gestalt Analysis: Correct+Acceptable	263	86	117	75	259	85	134	84
Q40 Taking Tums-Correct	246	80	117	75	255	84	126	79
Gestalt Analysis: Correct	241	79	114	74	253	83	123	77
Gestalt Analysis: Acceptable	36	12	22	14	30	10	17	11
Gestalt Analysis: Correct+Acceptable	277	90	136	88	283	93	140	88
Q18 OTC Cough drops-Correct	244	79	101	65	254	84	126	79
Gestalt Analysis: Correct	241	79	97	63	249	82	125	78
Gestalt Analysis: Acceptable	31	10	22	14	14	5	11	7
Gestalt Analysis: Correct+Acceptable	272	89	119	77	263	87	136	85

Reviewer's Comment

Many of the respondents had difficulty answering questions that involved information not found on the label. MRL described that these questions were added to the questionnaire in order to assess how well subjects make decisions about use of the product based on real life scenarios that are not described on the label (e.g. taking an antacid for an episode of heart burn). In many cases the respondents answered that the individual should talk to their doctor when asked why they answered the way they did. These responses were considered acceptable by MRL. The combined results of the correct and acceptable responses improved the range of correct responses considerably from 59-79% to 75-93%. Given that the information to contact a doctor was in response to an open-ended question, it is reasonable to consider these responses acceptable.

Conclusions

The study and the study questionnaire were well designed and did not appear to introduce bias, although it is unclear if participants had enrolled in more than one study. 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. A strength of the study design was that correct answers were validated by responses to the open-ended question "why do you say that?" In most cases the numbers of correct answers after validation were less by eliminating respondents who guessed.

There were some areas of the label that were adequately understood (Overall High Percentages of Correct Responses) and others that were poorly understood (Overall Low Percentages of Correct Responses):

Overall High Percentages of Correct Responses:

Comprehension of the absolute contraindications (allergy to lovastatin, pregnancy, and breast feeding) was adequate with greater than 90% gestalt correct responses for all of these messages. The range of gestalt correct responses for the pregnancy warning was 94-98% however, five out of the six women who answered the pregnancy question incorrectly were under the age of 55. Reasons for answering incorrectly primarily included inability to locate the warning on the label. Because lovastatin is a pregnancy category X drug, the number of correct responses needs to be close to 100%.

The muscle warning was well understood (range of gestalt correct responses was 96-98%). Further testing of the muscle warning was performed in the Muscle Warning Comprehension Study #088.

Most respondents understood the indication (96-97% gestalt correct responses).

Most respondents understood the labeled directions to take one table at a time, once a day (91-96% correct responses). Of those who answered incorrectly, the highest daily dose described by one low-literate respondent was 180 mg. Two respondents described a total daily dose of 80 mg. The remaining respondents who answered incorrectly described a total daily dose of 40 mg.

The ability to understand the appropriate age to be in order to take Mevacor ™ daily was adequate when the acceptable answers were added to the correct answers (87-94%). Most of the respondent's answers were considered acceptable if they stated that a person needs to talk to their doctor. This is correct according to the Drug facts label, however the label has conflicting statements: On the Principle Display Panel and on the flow diagram outside the Drug Facts label, the age statement is worded as an absolute contraindication ("This product is only for" and "You must be") whereas in Drug Facts the age statement is under the subheading "Ask a doctor before use if you" which is not an absolute contraindication. Although age is a Framingham risk factor, the primary issue from an adverse event perspective relates to pregnancy category X for women who may be pregnant or who may become pregnant should not use this product. As stated above, the study did not test the concept of a woman who may become pregnant which is a major deficiency considering the pregnancy category X status of the drug.

Overall the respondents understood when to talk to a doctor or pharmacist before starting Mevacor™ Daily (87-94%), with two exceptions: questions on the statements regarding oral antibiotics and large amounts of grapefruit juice in the low literate populations (74-79%). It is unclear why the low literate populations tested lower on these two questions because they were able to comprehend similar messages on the label (e.g. ask doctor or pharmacist before use if you are taking oral antifungals 87% for the LDL-C label and 90% for the Total-C label).

Most of the respondents understood the need to reduce the amount of cholesterol in the diet before starting Mevacor™ Daily (range of correct responses 90-97%). However the need to continue life style modification after starting Mevacor™ Daily was not tested.

The number of correct responses to the question regarding what happens when someone stops Mevacor™ Daily was adequate for both the representative populations and low literate populations (81-86%).

Overall Low Percentages of Correct Responses:

The concept of how to make decisions to use Mevacor ™ Daily based on cholesterol numbers and risk factors may be a difficult concept to convey no matter how well a label is designed. The flow diagram created by MRL to assist the consumer on how to decide if the "product is right for you" appears to be clearly written and tested better in the pilot study than the chart diagram. With the exception of the question asking if it is ok to use Mevacor™ Daily if a person does not know their cholesterol numbers, the range of correct responses was low for all questions related to risk factors, LDL, HDL and total cholesterol. The results remain low even after acceptable responses are added to the correct responses (29-87%). The Total-C label tested better than the LDL-C label on questions related to cholesterol numbers (70-86% versus 64-78%). Only one question was asked about risk factors. The range of correct responses for this question (Lisa believed she has a heart disease risk because her mother had a heart attack at age 50) was 29-46%. Given these low numbers, it is likely that the number of respondents able to make an appropriate self-selection decision based on their risk factors and cholesterol numbers would also be low. Because this study was not designed to evaluate appropriate self-selection, the ability of these study populations to appropriately self-select is not known.

Respondents had difficulty understanding what to do when someone develops a new medical problem. The question asking what to do if someone develops kidney disease was designed to test the understanding of the labeled statement "When using this product talk to a doctor if there is any change in your health, such as a new prescription medicine or new medical condition". The range of correct responses was 72-82%. This statement may need to be simplified and strengthened.

Many respondents did not understand when to take Mevacor ™ Daily ("with your evening meal"). The range of correct responses was 69-83%.

Overall the concepts related to cholesterol testing were not well understood (range of gestalt correct responses were 45-89%). The low literate populations had difficulty understanding that cholesterol testing should be performed prior to starting Mevacor ™ Daily (range of gestalt correct responses 67-76%). More participants understood the need to retest (79-86%) then understood when to retest (45-62%). The range of gestalt correct responses was also low for the question on what to do if someone's cholesterol is not lower after 6 weeks (59-69%). There was only a slight improvement when acceptable answers were added (63-70%). These low scores on the ability to comprehend the messages regarding appropriate follow-up are concerning. It is important to note that the product label used in the actual use study (Consumer Use of OTC Mevacor -CUSTOM) was different than the one tested in the current Pivotal SELECT Label Comprehension study. The message for re-testing cholesterol on the package used in the CUSTOM Study was bold and underlined in red. The CUSTOM Study demonstrated that 71% of the subjects obtained a follow-up cholesterol test. Results from the label comprehension study that tested the label used in CUSTOM demonstrated that 71-87% of the respondents understood when to retest versus 45-62% in the SELECT label comprehension study where the message for re-testing cholesterol is not enhanced. This lack of enhancement may account for the poor comprehension. This is further supported when comparing comprehension of the message that describes what to do if cholesterol/LDL goal is not meet. This message was not enhanced with bold print or underlined in red in either the CUSTOM label or the SELECT labels. The comprehension of this message was poor for all the labels (54-68% for the CUSTOM label and 59-69% for the SELECT labels).

Many respondents had a difficult time locating the active ingredient on the label (78-81% correct responses). The active ingredient is located on the outside flap separate from the rest of the Drug Facts label. This may have contributed to the poor comprehension.

Many of the respondents had difficulty answering questions that involved information not found on the label (59-79%). However many appropriately stated that the person should talk to their doctor when they did not know the answer increasing the correct responses to 75-93%.

II. Study Title: Muscle Warning Comprehension Study #088

Purpose/Objective: To measure in-depth consumer comprehension of the warning about unexplained muscle pain, tenderness or weakness after starting Mevacor™ Daily contained in the Drug Facts and the internal package materials.

Study Background:
Results from the actual use study (CUSTOM-A Consumer Use Study of OTC Mevacor), demonstrated that only 75% of subjects who developed muscle pain made a correct decision about use of Mevacor OTC. In response to this deficiency, MRL took the following actions to enhance the muscle warning:

- Expanded the warning language to include explanatory text and consequences of not heeding the warning
- Tested the modified language with consumers via qualitative one-on-one and focus group sessions
- Developed a magnet for product users to place in a visible location to remind them about the product warnings
- Ensured that the identical warning language used in each of the three internal package materials: Quick Start guide, Patient Package Insert, and Magnet
- Highlighted the entire muscle warning text (in two different locations) in the Patient Package Insert in red type
- Added language to the Prescription Medication warning to link it to the muscle warning
- Pilot-tested the materials and questionnaire in a quantitative study conducted on 80 respondents.

February and March 2007 MRL conducted a muscle warning label comprehension study designed to focus on the internal package materials and the degree to which they successfully communicate the specific warnings about unexplained muscle pain, weakness or tenderness. MRL states that although the muscle pain message attained a high score in the Pivotal SELECT Label Comprehension Study, MRL felt it was important to assess the impact of the entire set of muscle pain warnings contained outside and within the package.

Study Design:
The study was a one group design utilizing the LDL-C version of the nonprescription lovastatin package, label, and internal materials. For this study, the Sponsor chose to only test one label paradigm because the muscle warning for both the Total-C label and the LDL-C label are the same. The internal package materials included everything except the Drug Facts label. The muscle warning is located in several areas: (1) under the ***Warnings*** heading of the Drug Facts label, (2) in the Quick Start Guide, (3) on a magnet, and (4) in the insert/brochure (see Figures 4-

7). MRL states that the label used was nearly identical to the one tested in the Self Evaluation of Lovastatin to Enhance Cholesterol Treatment (SELECT) Study #086.

Figure 4: Muscle Warning: Drug Facts Label

Stop use and ask a doctor if you develop any unexplained muscle pain, weakness or tenderness. This can be a sign of a rare but serious side effect.

Figure 5: Muscle Warning: Quick Start Guide

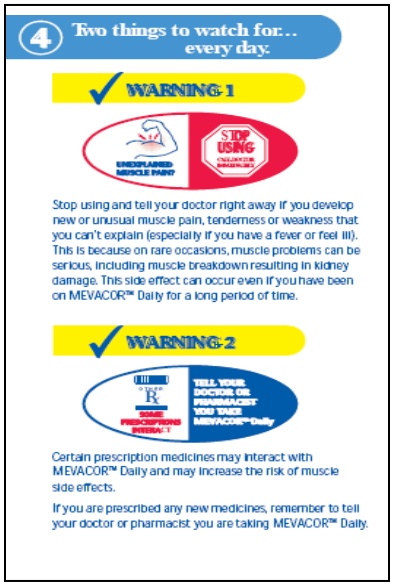


Figure 6: Muscle Warning: Magnet

Figure 7: Muscle Warning: Insert/Brochure

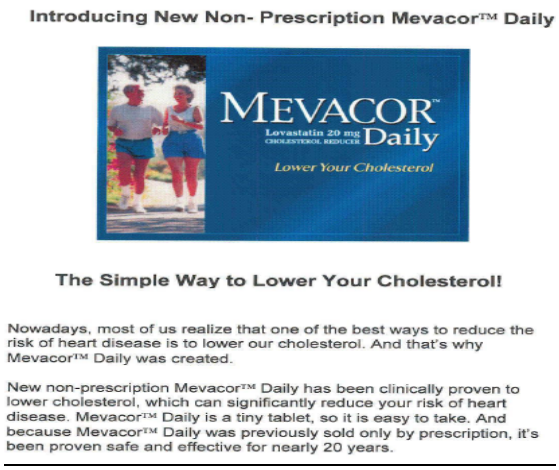
What are the side effects of MEVACOR™ Daily?

The active ingredient in MEVACOR™ Daily has been generally well-tolerated. Side effects have usually been mild. However, as with most drugs, serious side effects may occur. If the following or any other side effects occur while taking MEVACOR™ Daily, stop use and talk to your doctor right away.

- Stop using and tell your doctor right away if you develop new or unusual muscle pain, tenderness or weakness that you can't explain (especially if you have a fever or feel ill). This is because on rare occasions, muscle problems can be serious, including muscle breakdown resulting in kidney damage. This side effect can occur even if you have been on MEVACOR™ Daily for a long period of time.

Recruitment/Screening: Potential respondents were approached on the mall floor and administered a screener questionnaire and asked their level of cholesterol concern. Respondents who met the eligibility criteria and were either extremely or very concerned about their cholesterol where then shown a brief description of Mevacor™ Daily (see Figure 8 submitted by MRL). Those who indicated that they would either definitely, probably or might consider using Mevcor™ Daily were enrolled into the study.

Figure 8: Recruitment Material



Inclusion Criteria:

- Age
  - Men 40 and older
  - Women 50 and older
- Must be extremely or very concerned about cholesterol (on a 4 point scale of extremely, very, somewhat and not at all concerned)
- Must say definitely, probably, or might-might not consider using Mevacor ™ Daily (on a 4 point scale of definitely, probably, might-might not, definitely would not consider using)
- For low literacy respondents: Mispronounces or fails to pronounce six or more words on the REALM test (corresponding to an 8th grade reading level or below)

Exclusion Criteria:

- Participation in a market research survey in the mall in the past 3 months
- Employment of respondent, family or close friends in the following areas
  - By an advertising agency
  - By a market research company
  - By a company that processes or manufactures pharmaceutical, medical, or healthcare products
  - As a physician, nurse or pharmacist
- Reading glasses needed but not available

Reviewer's Comment

As with the Pivotal SELECT Label Comprehension Study, the exclusion criteria for this study only precluded someone from participating if he/she had participated in a market research survey in the mall in the past 3 months. It did not preclude anyone from participating if they had participated in previous label comprehension studies (including the Pre-SELECT Label Comprehension) or actual use studies for Mevacor. If someone had participated in another Mevacor study, their responses are potentially biased due to learning that may have occurred from participating in previous studies. It appears from the data submitted by MRL (see general information in the background section) that three subjects participated in both the Pre-SELECT Label Comprehension Study and the Muscle Warning Label Comprehension Study and two subjects participated in the Pivotal SELECT Label Comprehension and the Muscle Warning Label Comprehension Study. Ideally, these 5 subjects should be removed and the data reanalyzed, however it is unlikely that removing these 5 subjects would change the outcome of the study.

Study Sites:
The study was conducted in 20 geographically and demographically dispersed malls across the country. Figure 9 is a list of the study locations.

Figure 9: Study Locations

01( ) Boston, MA	06( ) Cleveland, OH	11( ) New York, NY	16( ) San Antonio, TX
02( ) Bridgeport, CT	07( ) Colorado Springs, CO	12( ) Philadelphia, PA	17( ) San Francisco, CA
03( ) Buffalo, NY	08( ) Houston, TX	13( ) Phoenix, AZ	18( ) Seattle, WA
04( ) Chicago, IL	09( ) Indianapolis, IN	14( ) Portland, OR	19( ) Springfield, MO
05( ) Cincinnati, OH	10( ) Los Angeles, CA	15( ) Raleigh-Durham, NC	20( ) Tampa, FL

Sample:
Sample size determination was based on a 90% and 95% confidence interval around the point estimate of 50%. The resulting value equated to a sample size of 300 representative respondents in each group and 100 low literacy respondents in each of the low literacy groups.

Reviewer's Comment
Sample size determination was the same for this study as was done for the Pivotal SELECT Label Comprehension. It is unclear why MRL chose to test 100 low literacy participants in this study and 150 low literate participants in the Pivotal SELECT Label Comprehension.

The total representative respondents in each group include both normal literate and low literate participants. The low literacy respondents in the low literacy groups include the low literate respondents from the total representative group plus low literate respondents recruited specifically to augment the total number of low literacy respondents.

In order to ensure that the sample would be representative of the broader population from an age and gender perspective, age and gender quotas were set to ensure equal distribution in each group.

Data collection method:
Data was collected through interviews. Study questions asked by the interviewer were in scenario format describing hypothetical individuals. Each scenario was typically asked in two parts: first the respondent was asked if it was "ok" or "not ok" for the hypothetical person to use or to continue to use Mevacor™ Daily, followed by an open-ended question asking the respondent why they gave the response they did. The open-ended responses were captured verbatim. False positive scenarios were also used to test whether respondents could make appropriate assessments of situations not specifically addressed on the label. In order not to bias the respondents to focus solely on the muscle warnings, the questionnaire also included some questions that did not specifically address the muscle warning. Many of these questions were the same questions used in the Pivotal SELECT Label Comprehension Study #087:

Q2b Indication
Q4 Doesn't know numbers
Q5 Liver disease
Q6 OTC cough drops
Q8 Unexplained muscle pain-
Q9- New prescription
Q10- Taking TUMS
Q11- New Dx Diabetes

The reminder of the questions were written specifically for this study:

Q2c Who should take it
Q2d Are there side effects
Q12b What symptoms indicate a side effect
(Q13a, 13b Probing question on side effects)
Q14a, 15a Can you develop Muscle pain after using a long time
Q14b, 15b What happens if you continue to use if you have muscle pain
Q14c, 15c How serious is the muscle pain warning
Q16a, 16b How likely would you contact a doctor
Q17a, 17b Would you remember the warning over time and why
Q18 Likelihood would read materials

Coding categories for each of the open-ended responses performed by Bruno and Ridgway Research Associates Inc. Their coding process is described as follows: Coding was based on least 50% of the verbatim responses. The codes were grouped by response category and placed into a code book. The coder read through every answer and coded the responses. The codebook was updated with new coding responses. Answers that did not fit into any of the codes in the codebook were listed in the miscellaneous list. A second coder checked the codes assigned to every answer. All discrepancies were discussed among the coders and project manager.

Reviewer's Comments
The recruitment material does not appear to pose any bias.

All questions in the questionnaire that required an "ok", "not ok", "don't know", "correct" or "incorrect" response were followed by an open-ended question asking the respondent why he/she said what they said. This method allowed for validation of correct responses.

Several of the muscle warning questions were leading:

1. *Question 12b, 13a and 13b: If respondents did not answer "muscle" or "muscular", or "body pain", or "fever" or "feeling ill" or "flu-like symptoms" after being asked the question "After Bill starts using the product, which symptoms, if any, might indicate that Bill is having a side effect from Mevacor Daily?"(Question 12a-12b) the respondents were asked a probing question (13a) "is there any sort of body pain or discomfort should alert a Mevacor Daily user that they could be experiencing a possible side effect?" If the respondent answers yes, they were asked "what sort of pain or discomfort should alert a Mevacor Daily user that they could be experiencing a possible side effect of Mevacor daily" (question 13b). The probing question teaches the respondent that "body pain" or discomfort" is a symptom of a side effect.*

2. *Question 16a asked "How likely is it that you, yourself, would contact a doctor if you felt these muscle symptoms when using Mevacor Daily?" The respondents were then read of list of choices: "Extremely likely", "very likely", "somewhat likely"," not too likely", or "not at all likely". This type of question generally causes a socially desirable response; the respondent answers either extremely likely or very likely because most probably believe this is what the interviewer would want to hear because it is the "right thing to*

do". An open ended question asking the respondent what they would do if they developed muscle pain while taking Mevacor™ Daily would have generated more reliable data.

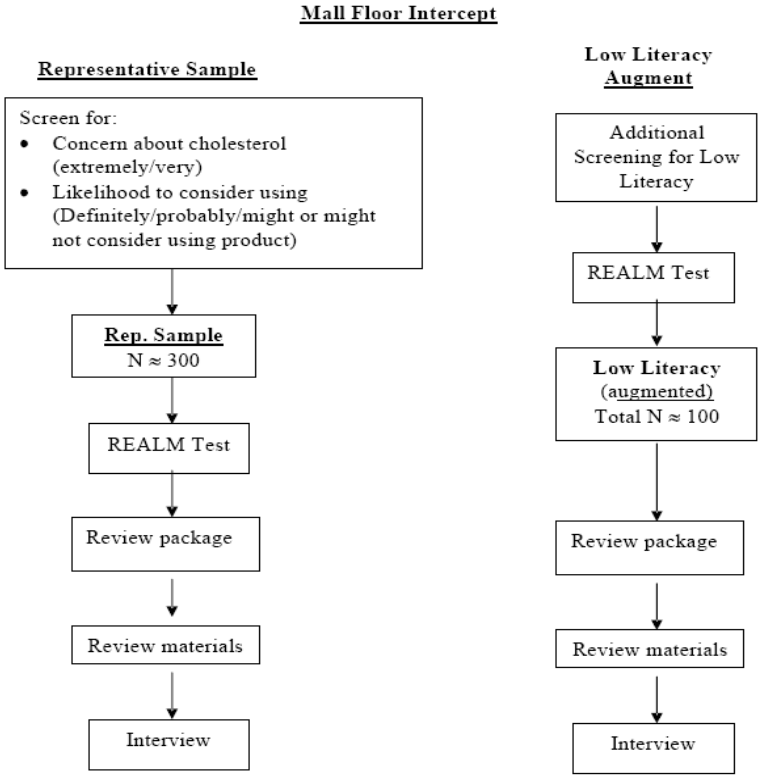
The remaining muscle warning questions do not appear to pose potential bias.

The standard coding process was employed without noted bias.

Study Plan:
Each interview averaged about 30 minutes. Respondents received $15 to participate. All participants were asked to sign a non-disclosure form. The Rapid Estimate of Adult Literacy (REALM) was used to determine the reading level of each Respondent. Respondents who missed 6 or more words (corresponding to an 8th grade reading level or lower) were classified as low literate.

Participants were provided with an empty package of Mevacor™ Daily and left alone to review the label information. They were asked to imagine that they have decided that the product is appropriate for them to use and so they buy it, take it home, and notice the internal package materials when they open the box. At that point of the interview, they were left alone with the materials (Quick Start Guide, the Patient Package Insert, and the Magnet). The review took 5-7 minutes followed by the interview. The Mevacor™ Daily package and materials were available throughout the interview. The study procedure is represented in Figure 10, provided by the MRL:

Figure 10: Study Procedure



Data Analysis:
The primary analysis was conducted on the percent of respondents in the representative sample who gave "correct", "acceptable", and "incorrect" responses.

Low Literacy subgroup (the low literacy subjects within the representative sample plus the augmented low literacy respondents) is statistically compared with the total representative sample.

Results:

Demographic Data:
Table 15, submitted by MRL, summarizes the demographics of the total sample and the augmented low literate sample:

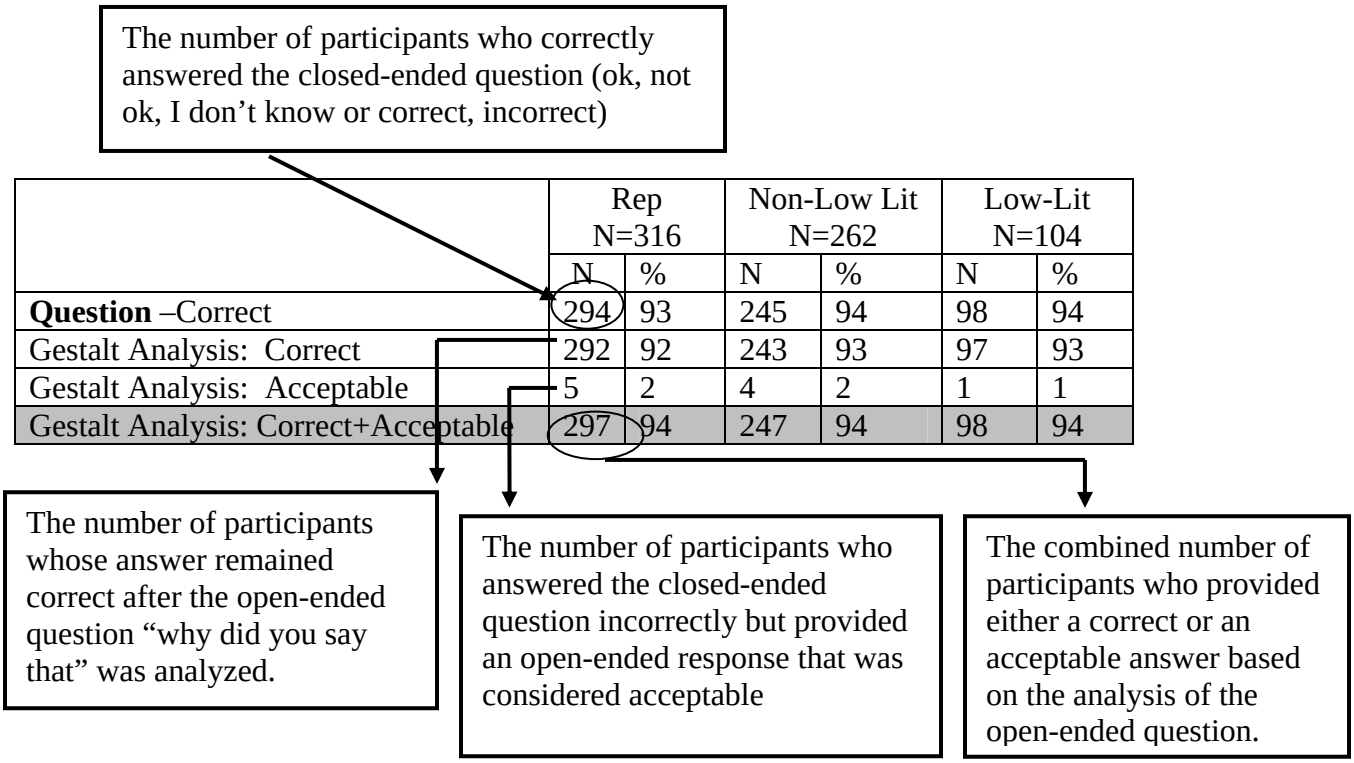
Table 15: Demographics

Demographics of Representative and Low Literacy Respondents

	Total Representative Sample		Total Low Literacy Sample	
Sample Size	N=316		N=104	
	N	%	N	%
Gender				
Male	160	51	47	45
Female	156	49	57	55
Age				
40-44	26	8	4	4
45-49	41	13	18	17
50-54	52	16	16	15
55-64	109	34	32	31
65+	88	28	34	33
Race				
Caucasian	251	79	64	62
Non-Caucasian	65	21	39	38
African-American	40	13	24	23
Hispanic	19	6	10	10
Asian/Pacific	5	2	5	5
Am. Indian	1	<1	0	0
Other	1	<1	1	1
Education				
HS incomplete or less	23	7	17	16
HS graduate	107	34	47	45
College	145	46	34	33
Some college	54	17	14	13
Degree/vocational	91	29	20	19
Post-college	39	12	4	4
Unspecified	2	1	2	2

Reviewer's Comments:
The demographic make up of the representative population and low literate population appear to be adequately diverse.

Results from the Interview Questions
MRL presented the results from the correct answers and the results from the "gestalt" correct answers in separate tables. For the purposes of this review, all of the correct and "gestalt" correct answers are presented in one table (Table 16) below. All data presented in Table 16 were obtained from data in Table 6-Table 27 submitted by MRL. The following is a description of the key elements contained in Table 16.



	Rep N=316		Non-Low Lit N=262		Low-Lit N=104	
	N	%	N	%	N	%
Question –Correct	294	93	245	94	98	94
Gestalt Analysis: Correct	292	92	243	93	97	93
Gestalt Analysis: Acceptable	5	2	4	2	1	1
Gestalt Analysis: Correct+Acceptable	297	94	247	94	98	94

MRL describes the following coding rules for responses that were not "clear-cut":

4. A participant's answer was considered <u>acceptable</u> if they provided the incorrect answer "not ok to use" for questions that asked about hypothetical situations not listed on the label and their response to the open-ended question was that the person should "talk to their doctor."
5. For questions that reference a portion of the label that directs the consumer to ask a doctor, a participant's answer was considered <u>acceptable</u> if they provided the correct answer "not ok to use" but their response to the open-ended question was "okay to use if they talk to their doctor."

<u>*Reviewer's Comments*</u>

Overall, based on the analysis of the open-ended questions, the percentage of gestalt correct answers were either the same as the percentage of correct answers or lower than the percentage of correct answers. Therefore, it is clear that some of the participants may have guessed correctly but when asked why they answered the way they did, they did not know the answer.

There were few cases in which the gestalt correct answers were slightly higher than the correct answer. MRL described that on a rare occasion, no response was recorded to the correct-incorrect answer or the ok, not ok, I don't know answer but there was a response recorded to the open-ended question. In these cases when the respondent answered the open-ended answer correctly, the percentage of total correct gestalt answers ended up being slightly higher than the percentage of total correct answers.

Table 16: Summary of Results

	Rep N=316		Non-Low Lit N=262		Low-Lit N=104	
	N	%	N	%	N	%
Q2b What does it treat-Correct	316	100	262	100	102	98
Q2c Who should take it-Correct	283	90	237	90	91	88
Q2d Are there side effects-Correct	301	95	251	96	100	96
Q4 Doesn't know numbers-Correct	294	93	245	94	98	94
Gestalt Analysis: Correct	292	92	243	93	97	93
Gestalt Analysis: Acceptable	5	2	4	2	1	1
Gestalt Analysis: Correct+Acceptable	297	94	247	94	98	94
Q5 Liver Disease-Correct	293	93	246	94	95	91
Gestalt Analysis: Correct	267	84	221	84	88	85
Gestalt Analysis: Acceptable	33	10	30	11	10	10
Gestalt Analysis: Correct+Acceptable	300	95	251	96	98	94
Q6 Using OTC cough drop-Correct	234	74	197	75	72	69
Gestalt Analysis: Correct	221	70	184	70	69	66
Gestalt Analysis: Acceptable	51	16	46	18	15	14
Gestalt Analysis: Correct+Acceptable	272	86	230	88	84	81
Q8 Unexplained muscle pain-Correct	309	98	258	98	101	97
Gestalt Analysis: Correct	308	97	257	98	101	97
Gestalt Analysis: Acceptable	1	<1	1	<1	0	0
Gestalt Analysis: Correct+Acceptable	309	98	258	98	101	97
Q9 New Prescription -Correct	266	84	225	86	86	83
Gestalt Analysis: Correct	275	87	234	89	84	81
Gestalt Analysis: Acceptable	12	4	9	3	7	7
Gestalt Analysis: Correct+Acceptable	287	91	243	93	91	88
Q10 Using TUMs-Correct	257	81	218	83	79	76
Gestalt Analysis: Correct	251	79	212	91	79	76
Gestalt Analysis: Acceptable	29	9	21	8	15	14**
Gestalt Analysis: Correct+Acceptable	280	89	233	89	94	90
Q11 New dx diabetes-Correct	283	90	238	91**	87	84
Gestalt Analysis: Correct	294	93	248	95	93	89
Gestalt Analysis: Acceptable	1	<1	1	<1	0	0
Gestalt Analysis: Correct+Acceptable	295	93	249	95	93	89

Table 16: Continued

	Rep N=316		Non-Low Lit N=262		Low-Lit N=104	
	N	%	N	%	N	%
12b What symptoms indicate side effect-Correct	297	94	248	95	96	92
Q14a, 15a Muscle pain after using long time -Correct	285	94	238	94	92	93
Q14b, 15b What happen if cont use with muscle pain -Correct	245	81	208	83	77	78
Q14c, 15c How serious is the muscle warning-Extremely serious	252	83	204	81	84	85
Q16a, 16b How likely contact Doctor –Extremely likely/very likely	286	95	239	95	94	95
Q17a Remember warning over time –Extremely likely/very likely	277	92	231	92	89	90
Q 17b Why do you say that?						
So serious it would be hard to forget	52	17	44	17	22	22
Kidney damage	40	13	34	13	13	13
I pay attention to warnings	78	26	60	24	32	32
Want to stay healthy	45	15	34	13	23	23
Pain would remind me	31	10	26	10	11	11
I would check problems with doctor	14	5	13	5	4	4
Package materials are clear	35	12	34	13	7	7
I have a good memory/easy to remember	21	7	18	7	3	3
Q18 Likelihood of reading materials –Extremely likely/very likely	290	92	242	92	95	91

*Statistical Difference at 95% CI
** Statistical Difference at 90% CI

Reviewer's Comments

The percentage of correct responses to questions related to the side effect of muscle pain and that a person should stop using Mevacor™ Daily if he/she develops unexplained muscle pain was high (97-98%).

Answers obtained from the probing questions for question 12b "is there any sort of body pain or discomfort that should alert a Mevacor Daily user that they could be experiencing a possible side effect? (13a)" followed by "what sort of body pain or discomfort should alert a Mevacor Daily user that they could be experiencing a possible side effect? (13b)" were provided by MRL in the following table:

Body Pain or Discomfort Probe Questions (Q 13a, Q13b)
(Among respondents not mentioning this in prior question)

	Representative		Non-Low Literacy		Low Literacy*	
Sample Size:	N=316		N=262		N=104	
	N	%	N	%	N	%
				A**		B**
Did not mention muscle or body pain or symptoms in Q12b	19	6	14	5	8	8
There is a body pain/discomfort	7	2	5	2	5	5
Muscle/Body Pain	5	2	4	2	3	3
Muscle/Muscle Issues	3	1	2	1	2	2
New pain/Fever/Flu-like symptoms	2	1	2	1	1	1
Did not mention muscle or body pain symptoms	2	1	1	<1	2	2
There is not a body pain/discomfort	5	2	3	1	2	2
Don't know	7	2	6	2	1	1

*Includes augmented respondents.
**Statistical significance tested in Columns A versus B. Capital letters indicate differences at the 95% confidence level and lower case letters indicate differences at the 90% confidence level.

Because these probing questions are leading, an assessment of these results was omitted from this review.

It is concerning that the percentage of correct responses were lower for the questions that address what will happen if someone who develops muscle pain continues using Mevacor™ Daily and the seriousness of the muscle pain warning (78-85%). The messages that convey the seriousness of muscle pain and what could happen if you continue using Mevacor™ Daily if you have muscle pain are written in the Quick start Guide, on the Magnet and in the Insert/Brochure (see Figures 5-7). These messages are written into a lengthy paragraph made up of several complex sentences. Even though these messages were enhanced using red text in the insert/brochure, comprehension remained low.

Because the question asking respondents how likely would he/she contact a doctor if he/she developed muscle pain while taking Mevacor™ Daily is leading and prompts respondents to provide a socially desirable answer, an assessment of the results were omitted from this review.

Questions 2b, 4, 5, 6, 8, 9, 10, 11 were the same questions asked in the Pivotal SELECT Label Comprehension Study #087. Results were very similar in both studies (see Table 17):

Table 17: Comparison of Results from Study #087 and Study #088

	Pivotal Study #087				***Muscle Study #088***			
	Rep N=307		*Low Lit N=155*		*Rep N=316*		*Low Lit N=104*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*
***Q2b Indication**-Correct*	*303*	*99*	*149*	*96*	*316*	*100*	*102*	*98*
***Q4 Doesn't know numbers**--Correct*	*299*	*97*	*140*	*90*	*292*	*92*	*97*	*93*
***Q5 Liver disease**-Correct*	*288*	*94*	*132*	*85*	*267*	*84*	*88*	*85*
***Q6 OTC cough drops**-Correct*	*241*	*79*	*97*	*63*	*221*	*70*	*69*	*66*
***Q8 Unexplained muscle pain**-Correct*	*300*	*98*	*149*	*96*	*308*	*97*	*101*	*97*
Q9- New prescription -Correct	*269*	*88*	*115*	*74*	*275*	*87*	*84*	*81*
Q10- Taking TUMS -Correct	*241*	*79*	*114*	*74*	*251*	*79*	*79*	*76*
Q11- New Dx Diabetes -Correct	*289*	*94*	*143*	*92*	*294*	*93*	*93*	*89*

The similarity in these results provides content validity for these questions. The percentage of correct results from the Pivotal SELECT Label Comprehension Study and the Muscle Warning Study differed by only one percentage point (96-98% versus 97-97%) for the question addressing unexplained muscle pain.

Conclusions

Several questions that focused on the muscle warning were leading and over prompted the respondents, therefore the results from these questions were excluded from this analysis. The other questions that focused on the muscle warning were well written and did not appear to introduce bias. Results from these questions demonstrate that most respondents understood that muscle pain is a side effect of lovastatin and a person who develops unexplained muscle pain should stop taking Mevacor™ Daily. It is not known if the respondents also understood the need to talk to a doctor if they develop muscle pain because the question used to assess this concept prompts respondents to provide a socially desirable answer. Not knowing if respondents understood this concept may not be as important as understanding the need to stop the drug. If someone has severe muscle pain or the pain does not resolve after stopping the drug it is likely he/she would seek medical attention.

It is concerning that the comprehension of the seriousness of the muscle pain warning and what could happen if someone who develops muscle pain continues to use Mevacor™ Daily was below 90%. These messages are very lengthy and not written in consumer-friendly language which may account for the decrease in comprehension.

Based on the exclusion criteria it is unclear if participants had enrolled in more than one Mevacor consumer study**.**

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2/21/07

APPENDIX D1

PACKAGE MATERIALS COMPREHENSION STUDY

Representative Sample -- Screening Questionnaire

RESPONDENT'S NAME: _____

ADDRESS:_____

CITY:_____STATE:_____ZIP:_____

PHONE #:(AREA CODE)_____(NUMBER)_____

SAMPLE
1(X) Representative

GENDER/AGE
1( ) Male 40-44
2( ) Male 45+
3( ) Female 50-54
4( ) Female 55+

WORDS INCORRECT (Q. L)
1( ) 0-5
2( ) 6 or more

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7455
2/21/07

PACKAGE MATERIALS COMPREHENSION STUDY
Representative Sample -- Screening Questionnaire

DATE OF INTERVIEW:_____

TIME START:_____TIME END:_____TOTAL LENGTH:_____

INTERVIEWER'S NAME:_____

RESCHEDULE DATE: _____ TIME: _____

GENDER/AGE
1( ) Male 40-44
2( ) Male 45+
3( ) Female 50-54
4( ) Female 55+

CITY:

01( ) Boston, MA	06( ) Cleveland, OH	11( ) New York, NY	16( ) Raleigh-Durham, NC
02( ) Bridgeport, CT	07( ) Colorado Springs, CO	12( ) Philadelphia, PA	17( ) San Antonio, TX
03( ) Buffalo, NY	08( ) Houston, TX	13( ) Phoenix, AZ	18( ) San Francisco, CA
04( ) Chicago, IL	09( ) Los Angeles, CA	14( ) Pittsburgh, PA	19( ) Seattle, WA
05( ) Cincinnati, OH	10( ) Louisville, KY	15( ) Portland, OR	20( ) Tampa, FL

(APPROACH MEN AND WOMEN WHO APPEAR TO BE 40/50 YEARS OF AGE AND OLDER.)

INTRODUCTION FOR MEN:
Hello, I'm _____ from Bruno and Ridgway Research Associates in Princeton, NJ. We are conducting a nationwide survey among men aged 40 and older regarding healthcare products. Are you in this age group or not?

( ) Yes - (CONTINUE)
( ) No - (TERMINATE AND TALLY) 1 2 3 4 5 6 7 8 9 0 X Y

INTRODUCTION FOR WOMEN:
Hello, I'm _____ from Bruno and Ridgway Research Associates in Princeton, NJ. We are conducting a nationwide survey among women aged 50 and older regarding healthcare products. Are you in this age group or not?

( ) Yes - (CONTINUE)
( ) No - (TERMINATE AND TALLY) 1 2 3 4 5 6 7 8 9 0 X Y

(INTERVIEWER: RECORD GENDER:)
1( ) Male
2( ) Female

A. What is your year of birth? _____
Y( ) Refused

(INTERVIEWER: CHECK BIRTH YEAR GRID TO FIND RESPONDENT'S AGE GROUP. RECORD AGE/GENDER GROUP ON PREVIOUS TWO PAGES OF SCREENER.)

(IF MEN UNDER 40 OR OVER QUOTA, TERMINATE AND TALLY.)
1 2 3 4 5 6 7 8 9 0 X Y

(IF WOMEN UNDER 50 OR OVER QUOTA, TERMINATE AND TALLY.)
1 2 3 4 5 6 7 8 9 0 X Y

(IF REFUSED BIRTH YEAR, CONTINUE. OTHERWISE SKIP TO Q. C.)

B. (HAND RESPONDENT CARD A) Please tell me which of these age groups you are in. (RECORD BELOW AND ON PREVIOUS TWO PAGES OF SCREENER.)

1( ) 40-44
2( ) 45-49
3( ) 50-54
4( ) 55-64
5( ) 65+

(IF MEN UNDER 40 OR OVER QUOTA, TERMINATE AND TALLY.)
1 2 3 4 5 6 7 8 9 0 X Y

(IF WOMEN UNDER 50 OR OVER QUOTA, TERMINATE AND TALLY.)
1 2 3 4 5 6 7 8 9 0 X Y

(TAKE BACK CARD A AND HAND CARD B)

C. To ensure we represent the opinions of all different types of people, we need to interview people in all races. This information is very important for the analysis of this study and is kept completely confidential. Which one or more of the following best describes your race? (MARK ALL THAT APPLY)

1( ) White/Caucasian
2( ) African-American
3( ) American Indian or Alaskan Native
4( ) Asian or Pacific Islander
5( ) Hispanic
X( ) Other (SPECIFY:) _____
Y( ) REFUSED

(TAKE BACK CARD B)

D. Have you participated in a market research survey in this mall within the past 3 months?

( ) Yes - (TERMINATE & TALLY) 1 2 3 4 5 6 7 8 9 0 X Y
( ) No - (CONTINUE)

E. Sometimes the type of work people do affects the products they buy. Are you, yourself, or is any member of your family or any close friend, employed . . . (READ LIST)?

	YES	NO
By an advertising agency	( )	( )
By a market research company	( )	( )
By a company that processes or manufactures pharmaceutical, medical or healthcare products	( )	( )
As a manager of a drugstore, supermarket or mass merchandising store	( )	( )
As a physician, nurse or pharmacist	( )	( )

(IF "YES" TO ANY OF THE ABOVE, TERMINATE & TALLY.) 1 2 3 4 5 6 7 8 9 0 X Y

(HAND CARD C)

F. I am going to read you a list of some specific health issues. After I read each one, please tell me the statement on this card that best describes how concerned you are about that issue *for yourself*. The first health issue is . . . ? (READ FIRST ITEM BELOW)

	Extremely Concerned	Very Concerned	Somewhat Concerned	Not At All Concerned
Your blood pressure level	1 ( )	2 ( )	3 ( )	4 ( )
Amount of fiber in your diet	1 ( )	2 ( )	3 ( )	4 ( )
Amount of fat in your diet	1 ( )	2 ( )	3 ( )	4 ( )
Your cholesterol level	1 ( )	2 ( )	( )	( )

IF BOXED ANSWER MARKED, TERMINATE AND TALLY
1 2 3 4 5 6 7 8 9 0 X Y

(TAKE BACK CARD C.)

G. Do you usually wear glasses when you read?

( ) Yes - (CONTINUE)
( ) No - (SKIP TO BOXED INSTRUCTIONS BEFORE Q. I)

H. Do you have your reading glasses with you today?

( ) Yes - (CONTINUE)
( ) No - (TERMINATE & TALLY) 1 2 3 4 5 6 7 8 9 0 X Y

(HAND RESPONDENT PRODUCT DESCRIPTION)

I. Here is a description of a new healthcare product that may soon be available in stores that sell nonprescription medicines. Carefully read the description, taking as much time as you need. Please tell me when you are finished. (CONTINUE WHEN RESPONDENT FINISHES)

(HAND CARD D)

J. Which statement on this card best describes how likely you would be to consider using MEVACOR™ Daily?

1( ) Definitely would consider
2( ) Probably would consider
3( ) Might or might not consider

→ CONTINUE

( ) Probably would not consider
( ) Definitely would not consider

→ TERMINATE AND TALLY
1 2 3 4 5 6 7 8 9 0 X Y

(TAKE BACK PRODUCT DESCRIPTION AND CARD D)

K. The reason for my questions is that I would like to get your opinion about MEVACOR™ Daily. The survey takes about 30 minutes, and I think you will find it interesting. We will pay you $_____ for your time. Would you be willing to help us?

( ) Yes - (CONTINUE)
( ) No - (TERMINATE & TALLY) 1 2 3 4 5 6 7 8 9 0 X Y)

INTERVIEWER: TAKE RESPONDENT TO INTERVIEWING ROOM.

(CONTINUE AT INTERVIEWING FACILITY. REMIND RESPONDENT TO WEAR READING GLASSES IF NEEDED)

L. We're going to begin with a word list of medical-related terms. These words are sometimes found on packages of medicines. I'd like you to read the words to me. We want to make sure that the people who write the labels and instructions for medicines use words people are familiar with. (HAND RESPONDENT WORD LIST.) I want to hear you read as many words as you can from this list. Begin with the first word and read each word aloud. If you come to a word you cannot read, do the best you can or say "pass" and go on to the next word. (AFTER WORD LIST IS COMPLETED, REMOVE LIST.)

INTERVIEWER:

- Follow along on the word list below.
- After each word is read, ***circle any word that is mispronounced or not attempted.***
  If a word is self-corrected, it counts as correct.
- If respondent takes more than 5 seconds on a word, say "pass" and point to the next word, if necessary, to move along. If respondent begins to miss every word, instruct to pronounce only known words.

NUMBER OF WORDS CIRCLED BELOW:

1( ) 0 - 5 words – (RECORD ON FRONT OF SCREENER)
2( ) 6 or more words – (RECORD ON FRONT OF SCREENER)

LIST 1	LIST 2	LIST 3
fat	fatigue	allergic
flu	pelvic	menstrual
pill	jaundice	testicle
dose	infection	colitis
eye	exercise	emergency
stress	behavior	medication
smear	prescription	occupation
nerves	notify	sexually
germs	gallbladder	alcoholism
meals	calories	irritation
disease	depression	constipation
cancer	miscarriage	gonorrhea
caffeine	pregnancy	inflammatory
attack	arthritis	diabetes
kidney	nutrition	hepatitis
hormones	menopause	antibiotics
herpes	appendix	diagnosis
seizure	abnormal	potassium
bowel	syphilis	anemia
asthma	hemorrhoids	obesity
rectal	nausea	osteoporosis
incest	directed	impetigo

CONTINUE WITH MAIN QUESTIONNAIRE

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2/28/07

APPENDIX D2

PACKAGE MATERIALS COMPREHENSION STUDY

Literacy Augment Sample -- Screening Questionnaire

RESPONDENT'S NAME: _____

ADDRESS:_____

CITY:_____STATE:_____ZIP:_____

PHONE #:(AREA CODE)_____(NUMBER)_____

SAMPLE
2(X) Literacy Augment

GENDER/AGE
1( ) Male 40-44
2( ) Male 45+
3( ) Female 50-54
4( ) Female 55+

WORDS INCORRECT (Q. L)
2(X) 6 or more

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2/28/07

PACKAGE MATERIALS COMPREHENSION STUDY
Literacy Augment Sample -- Screening Questionnaire

DATE OF INTERVIEW:_____

TIME START:_____TIME END:_____TOTAL LENGTH:_____

INTERVIEWER'S NAME:_____

RESCHEDULE DATE: _____ TIME: _____

GENDER/AGE
1( ) Male 40-44
2( ) Male 45+
3( ) Female 50-54
4( ) Female 55+

CITY:

01( ) Boston, MA	06( ) Cleveland, OH	11( ) New York, NY	16( ) Raleigh-Durham, NC
02( ) Bridgeport, CT	07( ) Colorado Springs, CO	12( ) Philadelphia, PA	17( ) San Antonio, TX
03( ) Buffalo, NY	08( ) Houston, TX	13( ) Phoenix, AZ	18( ) San Francisco, CA
04( ) Chicago, IL	09( ) Los Angeles, CA	14( ) Pittsburgh, PA	19( ) Seattle, WA
05( ) Cincinnati, OH	10( ) Louisville, KY	15( ) Portland, OR	20( ) Tampa, FL

(APPROACH MEN AND WOMEN WHO APPEAR TO BE 40/50 YEARS OF AGE AND OLDER.)

INTRODUCTION FOR MEN:
Hello, I'm _____ from Bruno and Ridgway Research Associates in Princeton, NJ. We are conducting a nationwide survey among men aged 40 and older regarding healthcare products. Are you in this age group or not?

( ) Yes - (CONTINUE)
( ) No - (TERMINATE AND TALLY) 1 2 3 4 5 6 7 8 9 0 X Y

INTRODUCTION FOR WOMEN:
Hello, I'm _____ from Bruno and Ridgway Research Associates in Princeton, NJ. We are conducting a nationwide survey among women aged 50 and older regarding healthcare products. Are you in this age group or not?

( ) Yes - (CONTINUE)
( ) No - (TERMINATE AND TALLY) 1 2 3 4 5 6 7 8 9 0 X Y

(INTERVIEWER: RECORD GENDER:)
1( ) Male
2( ) Female

A. What is your year of birth? _____
Y( ) Refused

(INTERVIEWER: CHECK BIRTH YEAR GRID TO FIND RESPONDENT'S AGE GROUP. RECORD AGE/GENDER GROUP ON PREVIOUS TWO PAGES OF SCREENER.)

(IF MEN UNDER 40 OR OVER QUOTA, TERMINATE AND TALLY.)
1 2 3 4 5 6 7 8 9 0 X Y

(IF WOMEN UNDER 50 OR OVER QUOTA, TERMINATE AND TALLY.)
1 2 3 4 5 6 7 8 9 0 X Y

(IF REFUSED BIRTH YEAR, CONTINUE. OTHERWISE SKIP TO Q. C.)

B. (HAND RESPONDENT CARD A) Please tell me which of these age groups you are in. (RECORD BELOW AND ON PREVIOUS TWO PAGES OF SCREENER.)

1( ) 40-44
2( ) 45-49
3( ) 50-54
4( ) 55-64
5( ) 65+

(IF MEN UNDER 40 OR OVER QUOTA, TERMINATE AND TALLY.)
1 2 3 4 5 6 7 8 9 0 X Y

(IF WOMEN UNDER 50 OR OVER QUOTA, TERMINATE AND TALLY.)
1 2 3 4 5 6 7 8 9 0 X Y

(TAKE BACK CARD A AND HAND CARD B)

C. To ensure we represent the opinions of all different types of people, we need to interview people in all races. This information is very important for the analysis of this study and is kept completely confidential. Which one or more of the following best describes your race? (MARK ALL THAT APPLY)

1( ) White/Caucasian
2( ) African-American
3( ) American Indian or Alaskan Native
4( ) Asian or Pacific Islander
5( ) Hispanic
X( ) Other (SPECIFY:) _____
Y( ) REFUSED

(TAKE BACK CARD B)

D. Have you participated in a market research survey in this mall within the past 3 months?

( ) Yes - (TERMINATE & TALLY) 1 2 3 4 5 6 7 8 9 0 X Y
( ) No - (CONTINUE)

E. Sometimes the type of work people do affects the products they buy. Are you, yourself, or is any member of your family or any close friend, employed . . . (READ LIST)?

	YES	NO
By an advertising agency	( )	( )
By a market research company	( )	( )
By a company that processes or manufactures pharmaceutical, medical or healthcare products	( )	( )
As a manager of a drugstore, supermarket or mass merchandising store	( )	( )
As a physician, nurse or pharmacist	( )	( )

(IF "YES" TO ANY OF THE ABOVE, TERMINATE & TALLY.) 1 2 3 4 5 6 7 8 9 0 X Y

(HAND CARD C)

F. I am going to read you a list of some specific health issues. After I read each one, please tell me the statement on this card that best describes how concerned you are about that issue *for yourself*. The first health issue is . . . ? (READ FIRST ITEM BELOW)

	Extremely Concerned	Very Concerned	Somewhat Concerned	Not At All Concerned
Your blood pressure level	1 ( )	2 ( )	3 ( )	4 ( )
Amount of fiber in your diet	1 ( )	2 ( )	3 ( )	4 ( )
Amount of fat in your diet	1 ( )	2 ( )	3 ( )	4 ( )
Your cholesterol level	1 ( )	2 ( )	( )	( )

IF BOXED ANSWER MARKED, TERMINATE AND TALLY
1 2 3 4 5 6 7 8 9 0 X Y

(TAKE BACK CARD C.)

G. Do you usually wear glasses when you read?

( ) Yes - (CONTINUE)
( ) No - (SKIP TO BOXED INSTRUCTIONS BEFORE Q. I)

H. Do you have your reading glasses with you today?

( ) Yes - (CONTINUE)
( ) No - (TERMINATE & TALLY) 1 2 3 4 5 6 7 8 9 0 X Y

(HAND RESPONDENT PRODUCT DESCRIPTION)

I. Here is a description of a new healthcare product that may soon be available in stores that sell nonprescription medicines. Carefully read the description, taking as much time as you need. Please tell me when you are finished. (CONTINUE WHEN RESPONDENT FINISHES)

(HAND CARD D)

J. Which statement on this card best describes how likely you would be to consider using MEVACOR™ Daily?

1( ) Definitely would consider
2( ) Probably would consider
3( ) Might or might not consider

→ CONTINUE

( ) Probably would not consider
( ) Definitely would not consider

→ TERMINATE AND TALLY
1 2 3 4 5 6 7 8 9 0 X Y

(TAKE BACK PRODUCT DESCRIPTION AND CARD D)

K. The reason for my questions is that I would like to get your opinion about MEVACOR™ Daily. However, I have one more question to ask you at our facility to see if you qualify for this opinion survey. It will take two more minutes of your time and I think you will find it interesting.

If you qualify for our opinion survey about MEVACOR™ Daily, it will take 20 minutes and we will pay you $15 for your time. Would you be willing to help us out?

( ) Yes - (CONTINUE)
( ) No - (TERMINATE & TALLY) 1 2 3 4 5 6 7 8 9 0 X Y

INTERVIEWER: TAKE RESPONDENT TO INTERVIEWING ROOM.

(CONTINUE AT INTERVIEWING FACILITY. REMIND RESPONDENT TO WEAR READING GLASSES IF NEEDED)

L. We're going to begin with a word list of medical-related terms. These words are sometimes found on packages of medicines. I'd like you to read the words to me. We want to make sure that the people who write the labels and instructions for medicines use words people are familiar with. (HAND RESPONDENT WORD LIST.) I want to hear you read as many words as you can from this list. Begin with the first word and read each word aloud. If you come to a word you cannot read, do the best you can or say "pass" and go on to the next word. (AFTER WORD LIST IS COMPLETED, REMOVE LIST.)

INTERVIEWER:

- Follow along on the word list below.
- After each word is read, ***circle any word that is mispronounced or not attempted.***
  If a word is self-corrected, it counts as correct.
- If respondent takes more than 5 seconds on a word, say "pass" and point to the next word, if necessary, to move along. If respondent begins to miss every word, instruct to pronounce only known words.

NUMBER OF WORDS CIRCLED BELOW:

1( ) 0 - 5 words – (SAY: "Thank you for your help." THEN TERMINATE & TALLY.)

1 2 3 4 5 6 7 8 9 0 X Y

2( ) 6 or more words – (SAY: "Congratulations. You qualify for our survey." THEN CONTINUE.)

LIST 1	LIST 2	LIST 3
fat	fatigue	allergic
flu	pelvic	menstrual
pill	jaundice	testicle
dose	infection	colitis
eye	exercise	emergency
stress	behavior	medication
smear	prescription	occupation
nerves	notify	sexually
germs	gallbladder	alcoholism
meals	calories	irritation
disease	depression	constipation
cancer	miscarriage	gonorrhea
caffeine	pregnancy	inflammatory
attack	arthritis	diabetes
kidney	nutrition	hepatitis
hormones	menopause	antibiotics
herpes	appendix	diagnosis
seizure	abnormal	potassium
bowel	syphilis	anemia
asthma	hemorrhoids	obesity
rectal	nausea	osteoporosis
incest	directed	impetigo

BRUNO and RIDGWAY Research Associates, Inc.
Lawrenceville, NJ 08648 Tel (609) 895-9889 Fax (609) 895-6669

APPENDIX D3

PACKAGE MATERIALS COMPREHENSION RESEARCH

(MAIN QUESTIONNAIRE)

Respondent's Name: _____

BRUNO and RIDGWAY Research Associates, Inc. 7455
Lawrenceville, NJ 08648 Tel (609) 895-9889 Fax (609) 895-6669

PACKAGE MATERIALS COMPREHENSION RESEARCH
(MAIN QUESTIONNAIRE)

(REMIND RESPONDENT TO WEAR GLASSES IF NEEDED FOR READING)

A. Before we continue, I'd like you to read and sign this nondisclosure agreement. (HAND RESPONDENT NONDISCLOSURE AGREEMENT AND A PEN. AFTER RESPONDENT SIGNS, CONTINUE.)

1a. We will be talking today about the new non-prescription over-the-counter healthcare product that you just read about in the product description. It's called MEVACOR™ Daily and it may soon be available in stores that sell non-prescription medicines. During this interview, I will be showing you a package and some materials being developed for MEVACOR™ Daily.

(TAKE OUT MEVACOR™ DAILY BOX. DO NOT GIVE TO RESPONDENT AT THIS TIME.)

1b. First, I would like you to look at this package as though you had picked it up in a store where you normally shop for non-prescription or over-the-counter medicines. This box contains no medicine inside.

I would like you to read the information on this package. I'm going to leave you alone while you do this, so you have time to concentrate.

(HAND RESPONDENT PACKAGE AND LEAVE AREA SO YOU ARE OUT OF SIGHT OF RESPONDENT. COME BACK AFTER 5 MINUTES.)

1c. Now imagine that you looked at the package in the store and decided that it **is** appropriate for you to use MEVACOR™ Daily, so you buy it and take it home. When you get home, you see that there is some information in the box, so you take it out to read it.

HAND PACKAGE MATERIALS:

- QUICK START GUIDE
- MAGNET
- PATIENT INFORMATION INSERT

1d. Please read this information as you would if you were going to start using this product. Like before, I'm going to leave you alone while you do this. After you are done reading the information, we will go through a series of questions that will help us to see how the information is doing in communicating product messages. This is not a test of your memory, so you will be able to look at the package and materials to answer my questions. You will have as much time as you need to read all the information.

(GIVE RESPONDENT ABOUT 5 MINUTES FOR REVIEW OF THE MATERIALS. KEEP BOX OUT ALSO.)

1e. I'm looking in on you to see how you are doing. I want to make sure you have enough time to read the materials before we go on with the interview. Do you want a few more minutes to continue reading the materials?

1( ) Yes – (SAY:) I'll check back with you in a few minutes → COME BACK IN 2 MINUTES AND RE-ASK. GIVE MORE TIME IF NEEDED
2( ) No – (CONTINUE)

2a. Now, I'm going to ask you some specific questions about this product. This is **not** a test of you. It is a way for us to see how well **these materials** explain important information about the product. Please remember that you can refer back to the package and any of the materials, so do not try to answer from memory or based on your own personal opinions or common sense.

2b. First, what is MEVACOR™ Daily used to treat? (DO NOT CLARIFY OR PROBE.)

_____

2c. In general, who should take Mevacor Daily?

_____

2d. **After** someone has started using Mevacor Daily, are there **any** possible side effects that someone should be aware of?

1( ) Yes
2( ) No

(TAKE OUT SMALL HANDOUT CARDS.)

3. Now I am going to ask you about the decisions that some people should make for themselves, **based on the information on the package label and in the materials you just read**.

I am going to give you several cards to read. They will describe different "made-up" or hypothetical people. Each hypothetical person has particular characteristics, and is separate from the previous ones. You will tell me if it is okay or not okay for each person to use Mevacor Daily, according to the information you have read. Other than the specific facts that you will hear about each person, you can assume that they meet all of the other requirements specified on the label or in the materials to use Mevacor Daily. I will read aloud as you follow along.

****PLACE ORANGE TENT CARD IN FRONT OF RESPONDENT UNTIL FURTHER NOTICE****

REMIND RESPONDENTS AS NEEDED...

- THAT THEY ARE ALLOWED TO LOOK AT THE PACKAGE AND OTHER MATERIALS TO ANSWER THE QUESTIONS, AND
- TO LOOK AT ORANGE TENT CARD IF THEY SAY "I DO NOT HAVE ENOUGH INFORMATION."

PLEASE WRITE THE COMPLETE RESPONSE FOR EACH "b" QUESTION. CLARIFY FULLY ALL RESPONSES. "She's fine", "He's OK," or "No problem" IS NOT ACCEPTABLE.

(ASK EACH QUESTION "(a)" and "(b)" IN TANDEM BEFORE MOVING ON TO NEXT QUESTION #.)

(HAND RESPONDENT CARD WITH Q. # THAT MATCHES QUESTION.
READ EACH QUESTION ALOUD WHILE RESPONDENT LOOKS AT HANDOUT CARD.)

Q#	Question	(a) Okay or Not Okay			(b) Why do you say that (IT IS OKAY/IT IS NOT OKAY/YOU DON'T KNOW) for (PERSON)?
		OK	Not OK	Don't know	
4	Kathleen is interested in lowering her cholesterol. She does not know her cholesterol numbers. Is it okay or not okay for Kathleen to start using Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____ _____
5	Ed has liver disease. He would like to lower his cholesterol. Is it okay or not okay for Ed to use Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
6	Al is using a nonprescription, OTC cough drop for a mild cough. He would like to lower his cholesterol. Is it okay or not okay for Al to use Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____

7. Up until now, we have been talking about people who needed to decide if Mevacor Daily is an appropriate product for them to **begin** to take. Now we are going to talk about what decisions people should make **after** they start using the product. Remember, other than the specific information you will read about each person, you can assume that they meet all of the other requirements to use Mevacor Daily. Also, remember that you can refer back to the package and other information to help you answer the questions.

Q#	Question	(a) Okay or Not Okay			(b) Why do you say that (IT IS OKAY/IT IS NOT OKAY/YOU DON'T KNOW) for (PERSON)?
		OK	Not OK	Don't Know	
8	Diane has been using Mevacor Daily for several weeks. She is now feeling muscle pain that she cannot explain. Is it okay or not okay for Diane to continue using Mevacor Daily?	Ok 1( )	Not OK 2( )	Don't Know Y( )	_____ _____
9	Bob has been using Mevacor Daily for several months. He developed an infection and went to the hospital's emergency room, where a doctor gave him a prescription oral antibiotic. Is it okay or not okay for Bob to continue using Mevacor Daily?	Ok 1( )	Not OK 2( )	Don't Know Y( )	_____ _____
10	Ellen has been taking Mevacor Daily for several months. She took Tums for indigestion that she got from eating spicy foods. Is it okay or not okay for Ellen to continue using Mevacor Daily?	Ok 1( )	Not OK 2( )	Don't Know Y( )	_____ _____
11	Frank has been using Mevacor Daily for several months. He was just diagnosed with diabetes. Is it okay or not okay for Frank to continue using Mevacor Daily?	Ok 1( )	Not OK 2( )	Don't Know Y( )	_____ _____

(REMOVE ORANGE TENT CARD)

12a. Now I'm going to ask you a few more questions about using Mevacor Daily. Again, keep in mind that you should answer these questions based on your understanding of the materials, and that you can refer back to them if you want to.

12b. Bill meets the requirements to take Mevacor Daily but he is concerned about possible side effects from this medicine. **After** Bill starts using the product, which symptoms, if any, might indicate that Bill is having a side effect from Mevacor Daily?

_____

_____

_____

IF RESPONDENT SAYS "muscle" or "muscular" ABOVE, MARK ON EXTENDED TAB BELOW AND SKIP TO THE INSTRUCTIONS BEFORE Q. 14a.

IF RESPONDENT SAYS SOMETHING SUCH AS "body pain," or "fever" or "feeling ill" or "flu-like symptoms," SKIP TO THE INSTRUCTIONS BEFORE Q. 14a.

IF RESPONDENT DOES NOT SAY ANY OF THOSE THINGS, CONTINUE WITH Q. 13a.

13a. Is there any sort of body pain or discomfort that should alert a Mevacor Daily user that they could be experiencing a possible side effect of Mevacor Daily, or not?

1( ) Yes – (CONTINUE)
2( ) No - (SKIP TO Q. 18)
Y( ) Don't know (SKIP TO Q. 18)

13b. What sort of body pain or discomfort should alert a Mevacor Daily user that they could be experiencing a possible side effect of Mevacor Daily?

_____

_____

_____

IF RESPONDENT SAYS "muscle" or "muscular" ABOVE, MARK ON EXTENDED TAB BELOW AND CONTINUE.

IF RESPONDENT SAYS SOMETHING SUCH AS "body pain," or "fever" or "feeling ill" or "flu-like symptoms," CONTINUE.

IF RESPONDENT DOES NOT SAY ANY OF THOSE THINGS, SKIP TO Q.18.

(CHECK EXTENDED TAB. IF "***MUSCLE***," MARKED CONTINUE. OTHERWISE SKIP TO Q. 15a)

14a. Now I will ask you a few more questions about these side effects that could occur when using Mevacor Daily. After someone has been using Mevacor Daily for a long period of time, do they still need to be concerned about these muscle side effects, or not?

1( ) Yes
2( ) No
Y( ) Don't know

14b. What could happen to someone who gets these muscle symptoms and still continues to use Mevacor Daily?

_____

_____

_____

14c. As you may know, there is a warning in the materials about muscle symptoms (POINT TO WARNING IN PACKAGE INSERT). Still thinking about the muscle warning in the Mevacor Daily materials, how serious of a *warning* do you, yourself, consider this to be? Please use a scale from 1 to 5 where 1 is not at all serious and 5 is extremely serious.

_____ → SKIP TO THE INSTRUCTIONS BEFORE Q. 16a

_____

15a. Now I will ask you a few more questions about these side effects that could occur when using Mevacor Daily. After someone has been using Mevacor Daily for a long period of time, do they still need to be concerned about these body pain side effects, or not?

1( ) Yes
2( ) No

15b. What could happen to someone who gets these body pain symptoms and still continues to use Mevacor Daily?

_____

_____

_____

15c. As you may know, there is a warning in the materials about body pain (POINT TO WARNING IN PACKAGE INSERT). Still thinking about the body pain warning in the Mevacor Daily materials, how serious of a *warning* do you, yourself, consider this to be? Please use a scale from 1 to 5 where 1 is not at all serious and 5 is extremely serious.

_____

(CHECK EXTENDED TAB. IF "***MUSCLE***," MARKED CONTINUE. OTHERWISE SKIP TO Q. 16b)

16a. How likely is it that you, yourself, would contact a doctor if you felt these muscle symptoms when using Mevacor Daily? Would you be....? (READ LIST)

1( ) Extremely likely
2( ) Very likely
3( ) Somewhat likely
4( ) Not too likely, or
5( ) Not at all likely to contact your doctor?

SKIP TO Q. 17a

16b. How likely is it that you, yourself, would contact a doctor if you felt these body pain symptoms when using Mevacor Daily? Would you be....? (READ LIST)

1( ) Extremely likely
2( ) Very likely
3( ) Somewhat likely
4( ) Not too likely, or
5( ) Not at all likely to contact your doctor?

17a. Still thinking about this warning, if you, yourself were to start using this product, how likely is it that you would remember this warning over a long period of time? Would you be....? (READ LIST)

1( ) Extremely likely,
2( ) Very likely,
3( ) Somewhat likely,
4( ) Not too likely, or
5( ) Not at all likely to remember this warning over a long period of time?

17b. Why do you say that?

_____

_____

18. And finally, thinking about your own personal habits and practices, if you were to buy Mevacor Daily for your own use, how likely is it that you would read one or more of these 3 materials from inside the package? Would you be...? (READ LIST)

1( ) Extremely likely
2( ) Very likely
3( ) Somewhat likely
4( ) Not too likely, or
5( ) Not at all likely to read any of those materials?

19. What is the last grade of school you completed? (RECORD ONLY ONE ANSWER. DO NOT READ LIST.)

1( ) Elementary school only (grades 1-8)
2( ) High school incomplete (grades 9-11)
3( ) High school graduate (grade 12)
( ) College – (PROBE:) Is that…(READ LIST)?
4( ) Vocational/Technical (after high school)
5( ) College incomplete
6( ) Associate's degree
7( ) Bachelor's degree
8( ) Postgraduate/advanced college degree
Y( ) Refused – (DO NOT READ)

---

20. INTERVIEWER: HAVE RESPONDENT FILL OUT SURVEY COMPLETION FORM.

THANK YOU FOR YOUR COOPERATION. YOUR OPINION COUNTS.

INTERVIEWER: STAPLE SCREENER AND MAIN QUESTIONNAIRE, NONDISCLOSURE AGREEMENT, AND "SURVEY COMPLETION" FORM TOGETHER.

THIS RESPONDENT MAY BE RECONTACTED DIRECTLY BY BRUNO AND RIDGWAY RESEARCH AS A PART OF THEIR NORMAL VERIFICATION PROCEDURES.

INTERVIEWER'S SIGNATURE:_____

1( ) Q. 12b/13b - MENTIONED MUSCLE

APPENDIX D1

BRUNO and RIDGWAY Research Associates, Inc. 7416
Lawrenceville, NJ 08648 Tel (609) 895-9889 Fax (609) 895-6669 12/06

LABEL COMPREHENSION STUDY

Screening Questionnaire

Representative Sample

RESPONDENT'S NAME: _____

ADDRESS:_____

CITY:_____STATE:_____ZIP:_____

PHONE #:(AREA CODE)_____(NUMBER)_____

CELL:
1( ) Yellow
2( ) Green

SAMPLE
1(X) Representative

BRUNO and RIDGWAY Research Associates, Inc.
Lawrenceville, NJ 08648 Tel (609) 895-9889 Fax (609) 895-6669

7416
12/06

CELL:
1( ) Yellow
2( ) Green

SAMPLE
1(X) Representative

RACE (Q. C):
1( ) Hispanic

WORDS INCORRECT (Q. M)
1( ) 0-5
2( ) 6 or more

GENDER
1( ) Male
2( ) Female

AGE GROUP (Q. A/B)
1( ) 18-34
2( ) 35-44
3( ) 45-54
4( ) 55+

LABEL COMPREHENSION STUDY
Screening Questionnaire
Representative Sample

DATE OF INTERVIEW:_____

TIME START:_____TIME END:_____TOTAL LENGTH:_____

INTERVIEWER'S NAME:_____

RESCHEDULE DATE: _____ TIME: _____

CITY:

01( ) Boston, MA	06( ) Cleveland, OH	11( ) New York, NY	16( ) San Antonio, TX
02( ) Bridgeport, CT	07( ) Colorado Springs, CO	12( ) Philadelphia, PA	17( ) San Francisco, CA
03( ) Buffalo, NY	08( ) Houston, TX	13( ) Phoenix, AZ	18( ) Seattle, WA
04( ) Chicago, IL	09( ) Indianapolis, IN	14( ) Portland, OR	19( ) Springfield, MO
05( ) Cincinnati, OH	10( ) Los Angeles, CA	15( ) Raleigh-Durham, NC	20( ) Tampa, FL

(APPROACH MEN AND WOMEN WHO APPEAR TO BE 18 YEARS OF AGE AND OLDER.)

INTRODUCTION:

Hello, I'm _____ from Bruno and Ridgway Research Associates in Princeton, NJ. We are conducting a nationwide survey among people aged 18 and older regarding healthcare products. Are you in this age group or not?

( ) Yes - (CONTINUE)
( ) No - (TERMINATE AND TALLY) 1 2 3 4 5 6 7 8 9 0 X Y

A. What is your year of birth? _____
Y( ) Refused

(INTERVIEWER: CHECK BIRTH YEAR GRID TO FIND RESPONDENT'S AGE GROUP.
RECORD AGE GROUP ON FRONT OF SCREENER.)

(IF UNDER 18 OR OVER QUOTA, TERMINATE AND TALLY.)
1 2 3 4 5 6 7 8 9 0 X Y

(IF REFUSED BIRTH YEAR, CONTINUE. OTHERWISE SKIP TO Q. C.)

B. (HAND RESPONDENT CARD A) Please tell me which of these age groups you are in. (RECORD BELOW AND ON FRONT OF SCREENER.)

1( ) 18-34
2( ) 35-44
3( ) 45-54
4( ) 55-64
5( ) 65+ - (RECORD AS 55+ ON FRONT OF SCREENER)

(IF UNDER 18 OR REFUSED AGE RANGE OR OVER QUOTA, TERMINATE AND TALLY.)

1 2 3 4 5 6 7 8 9 0 X Y

(TAKE BACK CARD A AND HAND CARD B)

C. To ensure we represent the opinions of all different types of people, we need to interview people in all races. This information is very important for the analysis of this study and is kept completely confidential. Which one or more of the following best describes your race? (MARK ALL THAT APPLY)

1( ) White/Caucasian
2( ) African-American
3( ) American Indian or Alaskan Native
4( ) Asian or Pacific Islander
5( ) Hispanic → RECORD ON PREVIOUS PAGE AS "HISPANIC"
X( ) Other (SPECIFY:) _____
Y( ) REFUSED

(TAKE BACK CARD B)

D. Have you participated in a market research survey in this mall within the past 3 months?

( ) Yes - (TERMINATE & TALLY) 1 2 3 4 5 6 7 8 9 0 X Y
( ) No - (CONTINUE)

E. Sometimes the type of work people do affects the products they buy. Are you, yourself, or is any member of your family or any close friend, employed . . . (READ LIST)?

	YES	NO
By an advertising agency	( )	( )
By a market research company	( )	( )
By a company that processes or manufactures pharmaceutical, medical or healthcare products	( )	( )
As a manager of a drugstore, supermarket or mass merchandising store	( )	( )
As a physician, nurse or pharmacist	( )	( )

(IF "YES" TO ANY OF THE ABOVE, TERMINATE & TALLY.) 1 2 3 4 5 6 7 8 9 0 X Y

(HAND CARD C)

F. I am going to read you a list of some specific health issues. After I read each one, please tell me the statement on this card that best describes how concerned you are about that issue *for yourself*. The first health issue is . . . ? (READ FIRST ITEM BELOW)

	Extremely Concerned	Very Concerned	Somewhat Concerned	Not At All Concerned
Your blood pressure level	1 ( )	2 ( )	3 ( )	4 ( )
Amount of fiber in your diet	1 ( )	2 ( )	3 ( )	4 ( )
Amount of fat in your diet	1 ( )	2 ( )	3 ( )	4 ( )
Your cholesterol level	1 ( )	2 ( )	( )	( )

IF BOXED ANSWER MARKED, TERMINATE AND TALLY
1 2 3 4 5 6 7 8 9 0 X Y

(TAKE BACK CARD C.)

G. Do you usually wear glasses when you read?

( ) Yes - (CONTINUE)
( ) No - (SKIP TO BOXED INSTRUCTIONS BEFORE Q. I)

H. Do you have your reading glasses with you today?

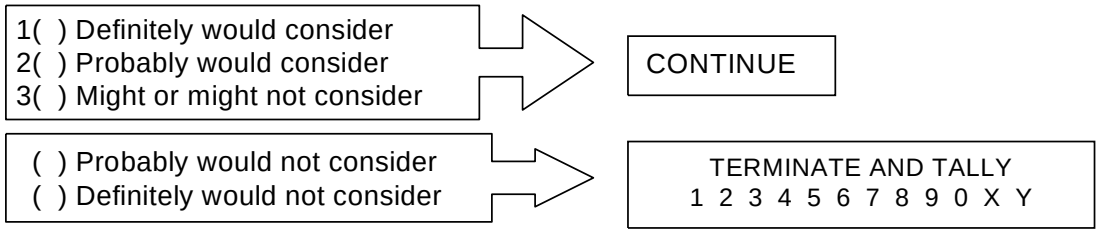
( ) Yes - (CONTINUE)
( ) No - (TERMINATE & TALLY) 1 2 3 4 5 6 7 8 9 0 X Y

(HAND RESPONDENT PRODUCT DESCRIPTION)

I. Here is a description of a new healthcare product that may soon be available in stores that sell nonprescription medicines. Carefully read the description, taking as much time as you need. Please tell me when you are finished. (CONTINUE WHEN RESPONDENT FINISHES)

(HAND CARD D)

J. Which statement on this card best describes how likely you would be to consider using MEVACOR™ OTC?



(TAKE BACK PRODUCT DESCRIPTION AND CARD D)

K. The reason for my questions is that I would like to get your opinion about MEVACOR™ OTC. The survey takes about 45 minutes, and I think you will find it interesting. We will pay you $20 for your time. Would you be willing to help us?

( ) Yes - (SKIP TO Q. M)
( ) No - (CONTINUE)

L. We would really like your opinions, so if you can come back another day this week, we will pay you an additional $5, that's $25 total for your time. Would you be willing to come back and help us at another time?

( ) Yes – (SCHEDULE INTERVIEW ON FRONT OF SCREENER)
( ) No - (TERMINATE & TALLY) 1 2 3 4 5 6 7 8 9 0 X Y

(CONTINUE AT INTERVIEWING FACILITY. REMIND RESPONDENT TO WEAR READING GLASSES IF NEEDED)

M. We're going to begin with a word list of medical-related terms. These words are sometimes found on packages of medicines. I'd like you to read the words to me. We want to make sure that the people who write the labels and instructions for medicines use words people are familiar with. (HAND RESPONDENT WORD LIST.) I want to hear you read as many words as you can from this list. Begin with the first word and read each word aloud. If you come to a word you cannot read, do the best you can or say "pass" and go on to the next word. (AFTER WORD LIST IS COMPLETED, REMOVE LIST.)

INTERVIEWER:

- Follow along on the word list below.
- After each word is read, ***circle any word that is mispronounced or not attempted.***
  If a word is self-corrected, it counts as correct.
- If respondent takes more than 5 seconds on a word, say "pass" and point to the next word, if necessary, to move along. If respondent begins to miss every word, instruct to pronounce only known words.

NUMBER OF WORDS CIRCLED BELOW:

1( ) 0 - 5 words – (RECORD ON FRONT OF SCREENER)
2( ) 6 or more words – (RECORD ON FRONT OF SCREENER)

LIST 1	LIST 2	LIST 3
fat	fatigue	allergic
flu	pelvic	menstrual
pill	jaundice	testicle
dose	infection	colitis
eye	exercise	emergency
stress	behavior	medication
smear	prescription	occupation
nerves	notify	sexually
germs	gallbladder	alcoholism
meals	calories	irritation
disease	depression	constipation
cancer	miscarriage	gonorrhea
caffeine	pregnancy	inflammatory
attack	arthritis	diabetes
kidney	nutrition	hepatitis
hormones	menopause	antibiotics
herpes	appendix	diagnosis
seizure	abnormal	potassium
bowel	syphilis	anemia
asthma	hemorrhoids	obesity
rectal	nausea	osteoporosis
incest	directed	impetigo

CONTINUE WITH MAIN QUESTIONNAIRE

BRUNO and RIDGWAY Research Associates, Inc. 7416
Lawrenceville, NJ 08648 Tel (609) 895-9889 Fax (609) 895-6669 12/06

APPENDIX D2

LABEL COMPREHENSION STUDY

Screening Questionnaire

Literacy Augment Sample

RESPONDENT'S NAME: _____

ADDRESS:_____

CITY:_____STATE:_____ZIP:_____

PHONE #:(AREA CODE)_____(NUMBER)_____

CELL:
1( ) Yellow
2( ) Green

SAMPLE
2(X) Literacy Augment

BRUNO and RIDGWAY Research Associates, Inc. 7416
Lawrenceville, NJ 08648 Tel (609) 895-9889 Fax (609) 895-6669 12/06

LABEL COMPREHENSION STUDY
Screening Questionnaire
Literacy Augment Sample

DATE OF INTERVIEW:_____

TIME START:_____TIME END:_____TOTAL LENGTH:_____

INTERVIEWER'S NAME:_____

RESCHEDULE DATE: _____ TIME: _____

CELL:
1( ) Yellow
2( ) Green

SAMPLE
2(X) Literacy Augment

WORDS INCORRECT (Q. L)
2(X) 6 or more

GENDER
1( ) Male
2( ) Female

AGE GROUP (Q. A/B)
1( ) 18-34
2( ) 35-44
3( ) 45-54
4( ) 55+

CITY:

01( ) Boston, MA	06( ) Cleveland, OH	11( ) New York, NY	16( ) San Antonio, TX
02( ) Bridgeport, CT	07( ) Colorado Springs, CO	12( ) Philadelphia, PA	17( ) San Francisco, CA
03( ) Buffalo, NY	08( ) Houston, TX	13( ) Phoenix, AZ	18( ) Seattle, WA
04( ) Chicago, IL	09( ) Indianapolis, IN	14( ) Portland, OR	19( ) Springfield, MO
05( ) Cincinnati, OH	10( ) Los Angeles, CA	15( ) Raleigh-Durham, NC	20( ) Tampa, FL

(APPROACH MEN AND WOMEN WHO APPEAR TO BE 18 YEARS OF AGE AND OLDER.)
INTRODUCTION:
Hello, I'm _____ from Bruno and Ridgway Research Associates in Princeton, NJ. We are conducting a nationwide survey among people aged 18 and older regarding healthcare products. Are you in this age group or not?

( ) Yes - (CONTINUE)
( ) No - (TERMINATE AND TALLY) 1 2 3 4 5 6 7 8 9 0 X Y

A. What is your year of birth? _____
Y( ) Refused

(INTERVIEWER: CHECK BIRTH YEAR GRID TO FIND RESPONDENT'S AGE GROUP.
RECORD AGE GROUP ON FRONT OF SCREENER.)

(IF UNDER 18 OR OVER QUOTA, TERMINATE AND TALLY.)
1 2 3 4 5 6 7 8 9 0 X Y

(IF REFUSED BIRTH YEAR, CONTINUE. OTHERWISE SKIP TO Q. C.)

B. (HAND RESPONDENT CARD A) Please tell me which of these age groups you are in. (RECORD BELOW AND ON FRONT OF SCREENER.)

1( ) 18-34
2( ) 35-44
3( ) 45-54
4( ) 55-64 - (RECORD AS 55+ ON FRONT OF SCREENER)
5( ) 65+

(IF UNDER 18 OR REFUSED AGE RANGE OR OVER QUOTA, TERMINATE AND TALLY.)

1 2 3 4 5 6 7 8 9 0 X Y

(TAKE BACK CARD A AND HAND CARD B)

C. To ensure we represent the opinions of all different types of people, we need to interview people in all races. This information is very important for the analysis of this study and is kept completely confidential. Which one or more of the following best describes your race? (MARK ALL THAT APPLY)

1( ) White/Caucasian
2( ) African-American
3( ) American Indian or Alaskan Native
4( ) Asian or Pacific Islander
5( ) Hispanic
X( ) Other (SPECIFY:) _____
Y( ) REFUSED

(TAKE BACK CARD B)

D. Have you participated in a market research survey in this mall within the past 3 months?

( ) Yes - (TERMINATE & TALLY) 1 2 3 4 5 6 7 8 9 0 X Y
( ) No - (CONTINUE)

E. Sometimes the type of work people do affects the products they buy. Are you, yourself, or is any member of your family or any close friend, employed . . . (READ LIST)?

	YES	NO
By an advertising agency	( )	( )
By a market research company	( )	( )
By a company that processes or manufactures pharmaceutical, medical or healthcare products	( )	( )
As a manager of a drugstore, supermarket or mass merchandising store	( )	( )
As a physician, nurse or pharmacist	( )	( )

(IF "YES" TO ANY OF THE ABOVE, TERMINATE & TALLY.) 1 2 3 4 5 6 7 8 9 0 X Y

(HAND CARD C)

F. I am going to read you a list of some specific health issues. After I read each one, please tell me the statement on this card that best describes how concerned you are about that issue *for yourself*. The first health issue is . . . ? (READ FIRST ITEM BELOW)

	Extremely Concerned	Very Concerned	Somewhat Concerned	Not At All Concerned
Your blood pressure level	1 ( )	2 ( )	3 ( )	4 ( )
Amount of fiber in your diet	1 ( )	2 ( )	3 ( )	4 ( )
Amount of fat in your diet	1 ( )	2 ( )	3 ( )	4 ( )
Your cholesterol level	1 ( )	2 ( )	( )	( )

IF BOXED ANSWER MARKED, TERMINATE AND TALLY
1 2 3 4 5 6 7 8 9 0 X Y

(TAKE BACK CARD C.)

G. Do you usually wear glasses when you read?

( ) Yes - (CONTINUE)
( ) No - (SKIP TO Q. I)

H. Do you have your reading glasses with you today?

( ) Yes - (CONTINUE)
( ) No - (TERMINATE & TALLY) 1 2 3 4 5 6 7 8 9 0 X Y

(HAND RESPONDENT PRODUCT DESCRIPTION)

I. Here is a description of a new healthcare product that may soon be available in stores that sell nonprescription medicines. Carefully read the description, taking as much time as you need. Please tell me when you are finished. (CONTINUE WHEN RESPONDENT FINISHES)

(HAND CARD D)

J. Which statement on this card best describes how likely you would be to consider using MEVACOR™ Daily?

1( ) Definitely would consider 2( ) Probably would consider 3( ) Might or might not consider	CONTINUE
( ) Probably would not consider ( ) Definitely would not consider	TERMINATE & TALLY 1 2 3 4 5 6 7 8 9 0 X Y

(TAKE BACK PRODUCT DESCRIPTION AND CARD D.)

K. The reason for my questions is that I would like to get your opinion about a healthcare product. The survey takes less than 5 minutes, and I think you will find it interesting. Would you be willing to help us out?

( ) Yes - (CONTINUE)
( ) No - (TERMINATE & TALLY) 1 2 3 4 5 6 7 8 9 0 X Y

INTERVIEWER: TAKE RESPONDENT TO INTERVIEWING ROOM.

(CONTINUE AT INTERVIEWING FACILITY. REMIND RESPONDENT TO WEAR READING GLASSES IF NEEDED)

L. We're going to begin with a word list of medical-related terms. These words are sometimes found on packages of medicines. I'd like you to read the words to me. We want to make sure that the people who write the labels and instructions for medicines use words people are familiar with. (HAND RESPONDENT WORD LIST.) I want to hear you read as many words as you can from this list. Begin with the first word and read each word aloud. If you come to a word you cannot read, do the best you can or say "pass" and go on to the next word. (AFTER WORD LIST IS COMPLETED, REMOVE LIST.)

INTERVIEWER:

- Follow along on the word list below.
- After each word is read, ***circle any word that is mispronounced or not attempted.***
  If a word is self-corrected, it counts as correct.
- If respondent takes more than 5 seconds on a word, say "pass" and point to the next word, if necessary, to move along. If respondent begins to miss every word, instruct to pronounce only known words.

NUMBER OF WORDS CIRCLED BELOW:

1( ) 0 - 5 words – (TERMINATE & TALLY) 1 2 3 4 5 6 7 8 9 0 X Y
2( ) 6 or more words – (CONTINUE)

LIST 1	LIST 2	LIST 3
fat	fatigue	allergic
flu	pelvic	menstrual
pill	jaundice	testicle
dose	infection	colitis
eye	exercise	emergency
stress	behavior	medication
smear	prescription	occupation
nerves	notify	sexually
germs	gallbladder	alcoholism
meals	calories	irritation
disease	depression	constipation
cancer	miscarriage	gonorrhea
caffeine	pregnancy	inflammatory
attack	arthritis	diabetes
kidney	nutrition	hepatitis
hormones	menopause	antibiotics
herpes	appendix	diagnosis
seizure	abnormal	potassium
bowel	syphilis	anemia
asthma	hemorrhoids	obesity
rectal	nausea	osteoporosis
incest	directed	impetigo

M. The reason for my questions is that I would like to get your opinion about MEVACOR™ Daily. The survey takes about another 40 minutes, and I think you will find it interesting. We will pay you $20 for your time. Would you be willing to help us?

( ) Yes - (RECORD RESPONDENT'S NAME ON "LITERACY AUGMENT QUOTA SHEET" AND CONTINUE WITH MAIN QUESTIONNAIRE)

( ) No - (CONTINUE)

N. We would really like your opinions, so if you can come back another day this week, we will pay you an additional $5, that's $25 total for your time. Would you be willing to come back and help us at another time?

( ) Yes – (SCHEDULE INTERVIEW ON FRONT OF SCREENER AND RECORD RESPONDENT'S NAME ON "LITERACY AUGMENT QUOTA SHEET")

( ) No - (TERMINATE AND TALLY) 1 2 3 4 5 6 7 8 9 0 X Y

CONTINUE WITH MAIN QUESTIONNAIRE

BRUNO and RIDGWAY Research Associates, Inc.
Lawrenceville, NJ 08648 Tel (609) 895-9889 Fax (609) 895-6669

APPENDIX D3a

PIVOTAL LABEL COMPREHENSION STUDY
(MAIN QUESTIONNAIRE)

Respondent's Name: _____

CELL:
1(X) Yellow (LDL)

2( ) Green (Total)

BRUNO and RIDGWAY Research Associates, Inc. 7416
Lawrenceville, NJ 08648 Tel (609) 895-9889 Fax (609) 895-6669

PIVOTAL LABEL COMPREHENSION STUDY
(MAIN QUESTIONNAIRE)

CELL:
1(X) **Yellow (Flow LDL)**
2( ) Green (Flow Total)

(REMIND RESPONDENT TO WEAR GLASSES IF NEEDED FOR READING)

A. Before we continue, I'd like you to read and sign this nondisclosure agreement. (HAND RESPONDENT NONDISCLOSURE AGREEMENT AND A PEN. AFTER RESPONDENT SIGNS, CONTINUE.)

1a. We will be talking today about the new over-the-counter healthcare product that you just read about in the product description. It's called MEVACOR™ Daily and it may soon be available in stores that sell non-prescription medicines. During this interview, I will be showing you a package being developed for MEVACOR™ Daily. I would like you to look at this package as though you had picked it up in a store where you normally shop for non-prescription or over-the-counter medicines.

You will have whatever time you feel you need to thoroughly review this package, and then we will go through a series of questions that will help us to see how the package is doing in communicating product information.

(TAKE OUT MEVACOR™ DAILY BOX WITH **YELLOW** DOT. DO NOT GIVE TO RESPONDENT AT THIS TIME.)

1b. This is the actual package that will be used for this product when it is available in stores. This box contains no medicine or any other materials inside. (DO NOT LET RESPONDENT EXAMINE PACKAGE YET).

I would like you to read the information on this package. I'm going to leave you alone while you do this, so you have time to concentrate. When I come back, I will ask you some questions about the product. This is not a test of your memory, so you will be able to look at the package to answer my questions. I will check back in a while to see how you are doing. You will have as much time as you need to read the package. (HAND RESPONDENT PACKAGE AND LEAVE AREA SO YOU ARE OUT OF SIGHT OF RESPONDENT)

(COME BACK AFTER 5 MINUTES)

1c. I'm looking in on you to see how you are doing. I want to make sure you have enough time to read over the package before we go on with the interview. Do you want a few more minutes to continue reading the package?

1( ) Yes – (SAY:) I'll check back with you in a few minutes → COME BACK IN 2 MINUTES AND RE-ASK. GIVE MORE TIME IF NEEDED
2( ) No – (CONTINUE)

(LEAVE PACKAGE OUT FOR ENTIRE INTERVIEW)

2a. Now, I'm going to ask you some specific questions about this product. This is not a test of you. It is a way for us to see how well **this package** communicates important information about the product. Please remember that you can refer back to the package, and do not try to answer from memory or based on your own personal opinions or common sense.

2b. First, what is MEVACOR™ Daily used to treat? (DO NOT CLARIFY OR PROBE.)

_____

2c. What is the active ingredient in MEVACOR™ Daily?

_____
_____

(TAKE OUT SMALL HANDOUT CARDS THAT MATCH COLOR OF QUESTIONNAIRE.)

3. Now I am going to ask you about the decisions that some people should make for themselves, based on the information on the package label.

I will be showing you cards that describe different hypothetical people. Each card will focus on a specific person with particular characteristics. You will tell me if it is okay or not okay for this person to use MEVACOR™ Daily right now, according to the package information. Other than the specific facts that you will hear about each person, you can assume that they would otherwise meet the requirements specified on the label to use Mevacor™ Daily.

****PLACE ORANGE TENT CARD IN FRONT OF RESPONDENT UNTIL FURTHER NOTICE****

REMIND RESPONDENTS AS NEEDED…

- THAT THEY ARE ALLOWED TO LOOK AT THE PACKAGE TO ANSWER THE QUESTIONS, AND
- TO LOOK AT ORANGE TENT CARD IF THEY SAY "I DO NOT HAVE ENOUGH INFORMATION."

PLEASE WRITE THE COMPLETE RESPONSE FOR EACH "b" QUESTION. CLARIFY FULLY ALL RESPONSES. "She's fine", "He's OK," or "No problem" IS NOT ACCEPTABLE.

(ASK EACH QUESTION "(a)" and "(b)" IN TANDEM BEFORE MOVING ON TO NEXT QUESTION #.)

(HAND RESPONDENT CARD WITH Q. # THAT MATCHES QUESTION.
READ EACH QUESTION ALOUD WHILE RESPONDENT LOOKS AT HANDOUT CARD.)

Q#	Question	(a) Okay or Not Okay			(b) Why do you say that (IT IS OKAY/IT IS NOT OKAY/ YOU DON'T KNOW) for (PERSON)?
		OK	Not OK	Don't know	
4	Warren has gotten an infection and his doctor has put him on an oral antibiotic. Warren wants to lower his cholesterol and would like to start using Mevacor Daily. Based on the package labeling, please answer by saying "okay" or "not okay" - is it okay or not okay for Warren to start using Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____ _____
5	Louis is interested in lowering his cholesterol. He has been having problems sleeping lately. Please answer by saying "okay" or "not okay" - Is it okay or not okay for Louis to use Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
6	Kathleen is interested in lowering her cholesterol. She does not know her cholesterol numbers. Is it okay or not okay for Kathleen to start using Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
7	Alice is pregnant with her second child. Is it okay or not okay for her to start using Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
8	Lisa is interested in lowering her cholesterol. Lisa believes she has a heart disease risk factor because her mother had a heart attack at age 50. Is it okay or not okay for Lisa to start using Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____

9a. How many times a day should someone take Mevacor Daily? _____

9b And how many tablets should someone take at one time? _____

9c. Here are some more cards that describe hypothetical people. As earlier, each card will focus on a specific person with particular characteristics. You will tell me if it is okay or not okay for this person to use MEVACOR™ Daily right now, according to the package information. Remember, other than the specific facts that you will hear about each person, you can assume that they would otherwise qualify to use Mevacor™ Daily. (REMIND RESPONDENTS AS NEEDED.)

(ASK EACH QUESTION "(a)" and "(b)" IN TANDEM BEFORE MOVING ON TO NEXT QUESTION #.
HAND RESPONDENT CARD WITH Q. # THAT MATCHES QUESTION.
READ EACH QUESTION ALOUD WHILE RESPONDENT LOOKS AT HANDOUT CARD.)

Q#	Question	(a) Okay or Not Okay			(b) Why do you say that (IT IS OKAY/IT IS NOT OKAY/ YOU DON'T KNOW) for (PERSON)?
		OK	Not OK	Don't know	
10	Mary is interested in lowering her cholesterol. She had a stroke a couple of months ago. Is it okay or not okay for Mary to start using Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
11	David wants to lower his LDL, or "bad", cholesterol, which is currently at 155. Is it okay or not okay for David to use Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
12	Ed has liver disease. He would like to lower his cholesterol. Is it okay or not okay for Ed to use Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
13	Sam had his cholesterol tested 3 years ago. Now he is interested in treating his cholesterol. Is it okay or not okay for Sam to start using Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____

Q#	Question	(a) Okay or Not Okay			(b) Why do you say that (IT IS OKAY/IT IS NOT OKAY/ YOU DON'T KNOW) for (PERSON)?
		OK	Not OK	Don't know	
14	Sheila has been trying to lower her cholesterol by swimming regularly and watching her diet. However, her LDL "bad" cholesterol is still 160. Is it okay or not okay for her to use Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
15	Emily has just gotten cholesterol test results that show her HDL "good" cholesterol to be at a level of 93. Is it okay or not okay for Emily to start using Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
16	Jim got his cholesterol tested without fasting first. Is it okay or not okay for Jim to use those test results to decide if he can use Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
17	Carol's LDL "bad" cholesterol is 190 and she would like to lower it. Is it okay or not okay for Carol to use Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
18	Al is using a nonprescription cough drop for a mild cough. He would like to lower his cholesterol. Is it okay or not okay for Al to use Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
19	Sara has been taking a medicine prescribed by her doctor to treat her elevated cholesterol level. Is it okay or not okay for Sara to start using Mevacor Daily along with her prescription cholesterol medicine?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____

20a. Is there a best time during the day to take Mevacor Daily, or not?

1( ) Yes – (CONTINUE)
2( ) No – (SKIP TO Q. 21)

20b. When is the best time during the day to take Mevacor Daily?

_____

21. Here are some more cards that describe hypothetical people. Again, each card will focus on a specific person with particular characteristics. You will tell me if it is okay or not okay for this person to use MEVACOR™ Daily right now, according to the package information. Remember, other than the specific facts that you will hear about each person, you can assume that they would otherwise qualify to use Mevacor™ Daily. (REMIND RESPONDENTS AS NEEDED.)

(ASK EACH QUESTION "(a)" and "(b)" IN TANDEM BEFORE MOVING ON TO NEXT QUESTION #.
HAND RESPONDENT CARD WITH Q. # THAT MATCHES QUESTION. READ EACH QUESTION ALOUD WHILE RESPONDENT LOOKS AT HANDOUT CARD.)

Q#	Question	(a) Okay or Not Okay			(b) Why do you say that (IT IS OKAY/IT IS NOT OKAY/ YOU DON'T KNOW) for (PERSON)?
		OK	Not OK	Don't know	
22	Rob would like to lower his cholesterol. His doctor told him that he is allergic to lovastatin. Is it okay or not okay for Rob to use Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
23	Peter gets gas from eating spicy foods once in a while. He is interested in lowering his cholesterol. Is it okay or not okay for him to use Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
24	Laurie has elevated cholesterol and would like to lower it. She is 38 years old. Is it okay or not okay for Laurie to start using Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____

Q#	Question	(a) Okay or Not Okay			(b) Why do you say that (IT IS OKAY/IT IS NOT OKAY/ YOU DON'T KNOW) for (PERSON)?
		OK	Not OK	Don't know	
25	Steve is interested in lowering his cholesterol. He enjoys grapefruit juice and drinks more than a quart every day. Is it okay or not okay for Steve to use Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
26	Mike has diabetes. He would like to lower his cholesterol. Is it okay or not okay for Mike to use Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
27	Janice has elevated cholesterol and would like to lower it. She is 68 years old. Is it okay or not okay for Janice to start using Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____

(TAKE BACK CARD 27 AND HAND CARD 28)

28. Normally Melanie eats foods that are high in cholesterol. Melanie has decided to use Mevacor Daily to lower her cholesterol. What, if anything, should Melanie do with her eating patterns before she starts to take Mevacor Daily?

_____

_____

29. Here are some more people to look over and tell me if it okay or not okay for this person to use MEVACOR™ Daily right now, according to the package information.

(ASK EACH QUESTION "(a)" and "(b)" IN TANDEM BEFORE MOVING ON TO NEXT QUESTION #.
HAND RESPONDENT CARD WITH Q. # THAT MATCHES QUESTION. READ EACH QUESTION ALOUD WHILE RESPONDENT LOOKS AT HANDOUT CARD.)

Q#	Question	(a) Okay or Not Okay			(b) Why do you say that (IT IS OKAY/IT IS NOT OKAY/ YOU DON'T KNOW) for (PERSON)?
		OK	Not OK	Don't know	
30	Helen had a baby two months ago and is currently breastfeeding. She is interested in controlling her cholesterol. Is it okay or not okay for her to start using Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
31	Jane's LDL "bad" cholesterol tested at a level of 115. Is it okay or not okay for Jane to use Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
32	Jerry got a fungal infection and is taking a prescription oral antifungal medicine. He would like to lower his cholesterol. Is it okay or not okay for Jerry to start using Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
33	Shirley would like to lower her cholesterol. She gets occasional tension headaches from the stresses of work. Is it okay or not okay for Shirley to start using Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
34	Ted, who is 35 years old, has elevated cholesterol. Is it okay or not okay for Ted to start using Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____

35. Up until now, we have been talking about people who needed to decide if Mevacor Daily is an appropriate product for them to take. Now we are going to talk about what decisions people should make <u>after</u> they start using the product.

(ASK EACH Q 36a AND 36b IN TANDEM BEFORE MOVING ON TO NEXT QUESTION #.
HAND RESPONDENT CARD WITH Q. # THAT MATCHES QUESTION. READ EACH QUESTION ALOUD WHILE RESPONDENT LOOKS AT HANDOUT CARD.)

Q#	Question	(a) Okay or Not Okay			(b) Why do you say that (IT IS OKAY/IT IS NOT OKAY/ YOU DON'T KNOW) for (PERSON)?
		OK	Not OK	Don't know	
36	Diane has been using Mevacor Daily for several weeks. She is now feeling muscle pain that she cannot explain. Is it okay or not okay for Diane to continue using Mevacor Daily?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____

(TAKE BACK CARD 36 AND HAND CARD 37)

37. Jeff has been using Mevacor Daily for several months. He was just diagnosed with kidney disease. What, if anything, should Jeff do now?

_____

_____

(TAKE BACK CARD 37 AND HAND CARD 38a)

38a. Gina has started to use Mevacor Daily. Will she need to get her cholesterol retested, or not?

1( ) Yes
2( ) No (Skip to 39)
Y( ) Don't know (Skip to 39)

(TAKE BACK CARD 38a AND HAND CARD 38b)

38b. Gina started taking Mevacor Daily **<u>today</u>** to lower her cholesterol. Based on the package labeling, how soon should Gina get a fasting cholesterol test to see if her LDL "bad" cholesterol has reached a healthy level?

_____

39. Here are a few final descriptions I want you to look at. Please tell me what decision each person should make after he or she starts using the product.

(ASK Q. 40a and 40b IN TANDEM BEFORE MOVING ON TO NEXT QUESTION #. HAND RESPONDENT CARD #40. READ QUESTION ALOUD WHILE RESPONDENT LOOKS AT HANDOUT CARD.)

Q#	Question	(a) Okay or Not Okay			(b) Why do you say that (IT IS OKAY/IT IS NOT OKAY/ YOU DON'T KNOW) for (PERSON)?
		OK	Not OK	Don't know	
40	Ellen has been taking Mevacor Daily for several months. She took Tums for indigestion that she got from eating spicy foods. Is it okay or not okay for Ellen to continue using Mevacor Daily?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____

(TAKE BACK CARD 40 AND HAND CARD 41)

41. Morris has been taking Mevacor Daily for 6 weeks to reduce his cholesterol. He has not yet reached the healthy level for his LDL cholesterol. What, if anything, should Morris do now?

_____

_____

(TAKE BACK CARD 41)

42. What, if anything, will happen to a person's cholesterol if that person who has been using Mevacor Daily stops taking it?

_____

(REMOVE ORANGE TENT CARD)

43. I now have some questions to ask you about your medical history.

44. (ASK ALL FEMALES)
Do any of the following apply to you?

1( ) You are pregnant
2( ) You are breast-feeding
3( ) You think you may become pregnant
Y( ) None of the above

45. As I read each of the following conditions, please tell me whether you, yourself, have been told that you have that condition. (READ EACH CONDITION BELOW. RECORD A "YES" OR "NO" FOR EACH.)

	YES	NO	DK
Ever had heart disease such as heart attack, angina [PRONOUNCED ann-JYE-na], heart bypass surgery, or a balloon angioplasty for your heart?	1( )	( )	( )
Ever had any kind of stroke, including mini-strokes and transient ischemic (I-SCEM-ic) attacks known as TIAs?	2( )	( )	( )
Currently have diabetes or high blood sugar?	3( )	( )	( )
Currently have liver disease such as hepatitis, or other liver problems	4( )	( )	( )

46. Have you been told that you are allergic to lovastatin [LO-va-stat-in], which is the active ingredient in MEVACOR™ Daily and prescription MEVACOR®?

1( ) Yes
2( ) No
Y( ) DON'T KNOW

47a. Are you currently taking any <u>prescription</u> drugs to lower blood lipids, cholesterol or triglycerides [try-GLISS-er-ides]?

1( ) Yes
2( ) No
→ SKIP TO Q. 48a

Y( ) DON'T KNOW – (CONTINUE)

(HAND CARD E)

47b. Are you currently taking any of the types of prescription medicines that are listed on this card?

1( ) Yes
2( ) No
Y( ) DON'T KNOW

(TAKE BACK CARD E AND HAND CARD F)

48a. Are you currently taking any of the types of prescription medicines that are listed on this card?

1( ) Yes – (CONTINUE)
2( ) No – (SKIP TO Q. 49a)
Y( ) DON'T KNOW – (SKIP TO Q. 49a)

(HAND "MEDICINE LIST Q. 48b")

48b. Please circle the prescription medicine or medicines you are currently taking. (TAKE BACK MEDICINE LIST 48b)

(TAKE BACK CARD F)

49a. Do you drink grapefruit juice on a daily basis?

1( ) Yes – (CONTINUE)
2( ) No – (SKIP TO Q. 50)

49b. Do you drink more than a quart of grapefruit juice on a daily basis?

1( ) Yes
2( ) No

---

50. What is the last grade of school you completed? (RECORD ONLY ONE ANSWER. DO NOT READ LIST.)

1( ) Elementary school only (grades 1-8)
2( ) High school incomplete (grades 9-11)
3( ) High school graduate (grade 12)
( ) College – (PROBE:) Is that…(READ LIST)?
4( ) Vocational/Technical (after high school)
5( ) College incomplete
6( ) Associate's degree
7( ) Bachelor's degree
8( ) Postgraduate/advanced college degree
Y( ) Refused – (DO NOT READ)

THANK YOU FOR YOUR COOPERATION. YOUR OPINION COUNTS.

INTERVIEWER: STAPLE SCREENER AND MAIN QUESTIONNAIRE, NONDISCLOSURE AGREEMENT, MEDICINE LIST 48b [IF APPLICABLE] AND "SURVEY COMPLETION" FORM TOGETHER.

THIS RESPONDENT MAY BE RECONTACTED DIRECTLY BY BRUNO AND RIDGWAY RESEARCH AS A PART OF THEIR NORMAL VERIFICATION PROCEDURES.

INTERVIEWER'S SIGNATURE:_____

BRUNO and RIDGWAY Research Associates, Inc. 7416
Lawrenceville, NJ 08648 Tel (609) 895-9889 Fax (609) 895-6669 11/29/28

APPENDIX D3b

PIVOTAL LABEL COMPREHENSION STUDY

(MAIN QUESTIONNAIRE: PAGES THAT DIFFER FROM LDL VERSION)

Respondent's Name: _____

CELL:

1( ) Yellow (LDL)

2(X) Green (Total)

BRUNO and RIDGWAY Research Associates, Inc. 7416
Lawrenceville, NJ 08648 Tel (609) 895-9889 Fax (609) 895-6669

PIVOTAL LABEL COMPREHENSION STUDY
(MAIN QUESTIONNAIRE)

CELL:
1( ) **Yellow (Flow LDL)**
2(X) Green (Flow Total)

(REMIND RESPONDENT TO WEAR GLASSES IF NEEDED FOR READING)

A. Before we continue, I'd like you to read and sign this nondisclosure agreement. (HAND RESPONDENT NONDISCLOSURE AGREEMENT AND A PEN. AFTER RESPONDENT SIGNS, CONTINUE.)

1a. We will be talking today about the new over-the-counter healthcare product that you just read about in the product description. It's called MEVACOR™ Daily and it may soon be available in stores that sell non-prescription medicines. During this interview, I will be showing you a package being developed for MEVACOR™ Daily. I would like you to look at this package as though you had picked it up in a store where you normally shop for non-prescription or over-the-counter medicines.

You will have whatever time you feel you need to thoroughly review this package, and then we will go through a series of questions that will help us to see how the package is doing in communicating product information.

(TAKE OUT MEVACOR™ DAILY BOX WITH **GREEN** DOT. DO NOT GIVE TO RESPONDENT AT THIS TIME.)

1b. This is the actual package that will be used for this product when it is available in stores. This box contains no medicine or any other materials inside. (DO NOT LET RESPONDENT EXAMINE PACKAGE YET).

I would like you to read the information on this package. I'm going to leave you alone while you do this, so you have time to concentrate. When I come back, I will ask you some questions about the product. This is not a test of your memory, so you will be able to look at the package to answer my questions. I will check back in a while to see how you are doing. You will have as much time as you need to read the package. (HAND RESPONDENT PACKAGE AND LEAVE AREA SO YOU ARE OUT OF SIGHT OF RESPONDENT)

(COME BACK AFTER 5 MINUTES)

1c. I'm looking in on you to see how you are doing. I want to make sure you have enough time to read over the package before we go on with the interview. Do you want a few more minutes to continue reading the package?

1( ) Yes – (SAY:) I'll check back with you in a few minutes → COME BACK IN 2 MINUTES AND RE-ASK. GIVE MORE TIME IF NEEDED
2( ) No – (CONTINUE)

9a. How many times a day should someone take Mevacor Daily? _____

9b And how many tablets should someone take at one time? _____

9c. Here are some more cards that describe hypothetical people. As earlier, each card will focus on a specific person with particular characteristics. You will tell me if it is okay or not okay for this person to use MEVACOR™ Daily right now, according to the package information. Remember, other than the specific facts that you will hear about each person, you can assume that they would otherwise qualify to use Mevacor™ Daily. (REMIND RESPONDENTS AS NEEDED.)

(ASK EACH QUESTION "(a)" and "(b)" IN TANDEM BEFORE MOVING ON TO NEXT QUESTION #.
HAND RESPONDENT CARD WITH Q. # THAT MATCHES QUESTION. READ EACH QUESTION ALOUD WHILE RESPONDENT LOOKS AT HANDOUT CARD.)

Q#	Question	(a) Okay or Not Okay			(b) Why do you say that (IT IS OKAY/IT IS NOT OKAY/ YOU DON'T KNOW) for (PERSON)?
		OK	Not OK	Don't know	
10	Mary is interested in lowering her cholesterol. She had a stroke a couple of months ago. Is it okay or not okay for Mary to start using Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
11	David wants to lower his total cholesterol, which is currently at 225. Is it okay or not okay for David to use Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
12	Ed has liver disease. He would like to lower his cholesterol. Is it okay or not okay for Ed to use Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
13	Sam had his cholesterol tested 3 years ago. Now he is interested in treating his cholesterol. Is it okay or not okay for Sam to start using Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____

Q#	Question	(a) Okay or Not Okay			(b) Why do you say that (IT IS OKAY/IT IS NOT OKAY/ YOU DON'T KNOW) for (PERSON)?
		OK	Not OK	Don't know	
14	Sheila has been trying to lower her cholesterol by swimming regularly and watching her diet. However, her Total cholesterol is still 230. Is it okay or not okay for her to use Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
15	Emily has just gotten cholesterol test results that show her HDL "good" cholesterol to be at a level of 93. Is it okay or not okay for Emily to start using Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
16	Jim got his cholesterol tested without fasting first. Is it okay or not okay for Jim to use those test results to decide if he can use Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
17	Carol's Total cholesterol is 270 and she would like to lower it. Is it okay or not okay for Carol to use Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
18	Al is using a nonprescription cough drop for a mild cough. He would like to lower his cholesterol. Is it okay or not okay for Al to use Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
19	Sara has been taking a medicine prescribed by her doctor to treat her elevated cholesterol level. Is it okay or not okay for Sara to start using Mevacor Daily along with her prescription cholesterol medicine?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____

29. Here are some more people to look over and tell me if it okay or not okay for this person to use MEVACOR™ Daily right now, according to the package information.

(ASK EACH QUESTION "(a)" and "(b)" IN TANDEM BEFORE MOVING ON TO NEXT QUESTION #.
HAND RESPONDENT CARD WITH Q. # THAT MATCHES QUESTION. READ EACH QUESTION ALOUD WHILE RESPONDENT LOOKS AT HANDOUT CARD.)

Q#	Question	(a) Okay or Not Okay			(b) Why do you say that (IT IS OKAY/IT IS NOT OKAY/ YOU DON'T KNOW) for (PERSON)?
		OK	Not OK	Don't know	
30	Helen had a baby two months ago and is currently breastfeeding. She is interested in controlling her cholesterol. Is it okay or not okay for her to start using Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
31	Jane's Total cholesterol tested at a level of 185. Is it okay or not okay for Jane to use Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
32	Jerry got a fungal infection and is taking a prescription oral antifungal medicine. He would like to lower his cholesterol. Is it okay or not okay for Jerry to start using Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
33	Shirley would like to lower her cholesterol. She gets occasional tension headaches from the stresses of work. Is it okay or not okay for Shirley to start using Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____
34	Ted, who is 35 years old, has elevated cholesterol. Is it okay or not okay for Ted to start using Mevacor Daily right now?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____

35. Up until now, we have been talking about people who needed to decide if Mevacor Daily is an appropriate product for them to take. Now we are going to talk about what decisions people should make after they start using the product.

(ASK EACH Q 36a AND 36b IN TANDEM BEFORE MOVING ON TO NEXT QUESTION #.
HAND RESPONDENT CARD 36. READ EACH QUESTION ALOUD WHILE RESPONDENT LOOKS AT HANDOUT CARD.)

Q#	Question	(a) Okay or Not Okay			(b) Why do you say that (IT IS OKAY/IT IS NOT OKAY/ YOU DON'T KNOW) for (PERSON)?
		OK	Not OK	Don't know	
36	Diane has been using Mevacor Daily for several weeks. She is now feeling muscle pain that she cannot explain. Is it okay or not okay for Diane to continue using Mevacor Daily?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____

(TAKE BACK CARD 36 AND HAND CARD 37)

37. Jeff has been using Mevacor Daily for several months. He was just diagnosed with kidney disease. What, if anything, should Jeff do now?

_____

_____

(TAKE BACK CARD 37 AND HAND CARD 38a)

38a. Gina has started to use Mevacor Daily. Will she need to get her cholesterol retested, or not?

1( ) Yes
2( ) No (Skip to 39)
Y( ) Don't know (Skip to 39)

(TAKE BACK CARD 38a AND HAND CARD 38b)

38b. Gina started taking Mevacor Daily **today** to lower her cholesterol. Based on the package labeling, how soon should Gina get a fasting cholesterol test to see if her Total cholesterol has reached a healthy level?

_____

39. Here are a few final descriptions I want you to look at. Please tell me what decision each person should make after he or she starts using the product.

(ASK Q. 40a and 40b IN TANDEM BEFORE MOVING ON TO NEXT QUESTION #. HAND RESPONDENT CARD #40. READ QUESTION ALOUD WHILE RESPONDENT LOOKS AT HANDOUT CARD.)

Q#	Question	(a) Okay or Not Okay			(b) Why do you say that (IT IS OKAY/IT IS NOT OKAY/ YOU DON'T KNOW) for (PERSON)?
		OK	Not OK	Don't know	
40	Ellen has been taking Mevacor Daily for several months. She took Tums for indigestion that she got from eating spicy foods. Is it okay or not okay for Ellen to continue using Mevacor Daily?	OK 1( )	Not OK 2( )	Don't know Y( )	_____ _____

(TAKE BACK CARD 40 AND HAND CARD 41)

41. Morris has been taking Mevacor Daily for 6 weeks to reduce his cholesterol. He has not yet reached the healthy level for his Total cholesterol. What, if anything, should Morris do now?

_____

_____

(TAKE BACK CARD 41)

42. What, if anything, will happen to a person's cholesterol if that person who has been using Mevacor Daily stops taking it?

_____

FDA Briefing Document
SELECT Study

NDA 21-213

Mevacor™ Daily (lovastatin) Tablets, 20 mg

Merck & Co., Inc.

Advisory Committee – December 13, 2007

Medical Reviewer: Linda Hu, M.D.

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1 EXECUTIVE SUMMARY

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Recommendations on regulatory action will be made after the Advisory Committee deliberations of 12/13/07.

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1.2.2 Required Phase 4 Commitments

1.2.3 Other Phase 4 Requests

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The initial NDA 21-213 for the OTC switch of Mevacor was submitted in 1999. This review covers only the results of the Self Evaluation of Lovastatin to Enhance Cholesterol Treatment (SELECT) Study (P086), which is included in the second resubmission of the NDA. The study is a self-selection study which evaluates the correctness of consumers' decisions whether a medication is appropriate for them to use. This study tested two labels, one based upon a Total-C treatment paradigm and the other based upon a LDL-C treatment paradigm. At an April 25, 2005 meeting with the Sponsor, the Agency confirmed that the treatment paradigm must be consistent with National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) Guidelines which use LDL-cholesterol as the basis for determining the need for cholesterol-lowering treatment. SELECT used scripted interviews to evaluate the correctness of participants' self-assessment (SA) and purchase decisions (PD), and it collected information to investigate the reasons why consumers made inconsistent or inappropriate decisions. Serum cholesterol and blood pressures were measured on participants after they made their self-selection and purchase decisions.

The SELECT labels were designed to minimize the proportion of women <55 years of age among the purchaser population, minimize the proportion of women of childbearing potential among the purchaser population, and minimize the proportion of low CHD risk purchasers. The LDL label paradigm is based on LDL cholesterol 130 to 170 mg/dL. The Total-C label paradigm uses total cholesterol 200 to 240 mg/dL which may be more familiar to consumers. Both label

paradigms have additional eligibility criteria based upon age, sex, risk factors, and other lipid values. Advertisements used for recruitment stated that it was "important to know your four cholesterol numbers: total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides …to participate in the study ." Subjects were also informed that they would be asked to decide whether the product is appropriate for them to use. This advertising may have recruited a more informed population with subjects who were more likely to know their cholesterol profiles and may have been primed to pay extra attention to information on the label. These actions may have improved the correct self-selection rate.

1.3.2 Efficacy

The participants in the SELECT study were typically well educated and middle class based upon income. More than 90% were high school graduates and 60% had some college. About 70% had health insurance. There were 1520 subjects randomized to the two study arms, 767 to the LDL-C paradigm arm and 753 to the Total-C paradigm arm. See Figure 1, Table 6 and Table 26.

The principal outcomes are summarized in Figure 2, Figure 3, Figure 4, and Figure 5. The rates of correct SA and PD responses were similar for the two label paradigms. About 20% of subjects were completely correct in their SA or PD = Yes responses for either of the two arms. The Sponsor analyzed the interview results to identify subjects who gave incorrect responses to SA and/or PD according to the label but whose open-ended responses nevertheless provided a rationale for their using the product; these ineligible subjects were said to be mitigated. The Sponsor found that almost half the ineligible subjects who incorrectly selected SA=Yes could be mitigated, raising the correct and mitigated proportion of subjects to about 50%. More detailed tabulations of SA and PD outcomes are found in Table 10, Table 11 and Table 12. Mitigation results are summarized in Table 8 and Table 9.

In addition, the Sponsor constructed several hierarchies of label eligibility criteria, whereby certain criteria they judged to be less clinically important could be waived. Several hierarchies were proposed, whereby the percent correct before mitigation ranged from about 21% to 80% depending on the hierarchy scheme (that is, depending on which specific label criteria are waived). Then the proportion of correct plus mitigated subjects could be raised to about 90% in the best case and to about 50% in the worst case. See Table 30, Table 31, or Table 32 for three examples.

The FDA review team constructed two additional hierarchies for each label paradigm, based upon a subset of the label criteria which were judged to be the most clinically important (age, not on lipid-lowering drugs, LDL-C, not on interacting medicines, risk factors). The percent correct for FDA Hierarchy 1, in the LDL arm (see Table 33), is 21%. The percent correct after mitigations in the hierarchy increased to 52.8%. For Hierarchy 2, in the LDL arm (Table 34), the percent correct is 17.8% with the percent correct increasing to 50.9% after mitigations. See also Table 35 and Table 36 for the Total-C arm.

The Medical Officer (MO) Comment after Table 11 summarizes the frequencies of ineligibilities for subjects in the LDL-C arm who said SA=Yes. For instance, a population of concern is subjects with a heart problem or heart disease; here 33 subjects out of 68 with heart disease, or

almost half, said the product was appropriate to use (SA=Yes). Also of concern is the prevalence for those already on medication to lower blood lipid, cholesterol, or triglycerides, again as shown for SA=Yes: 44 subjects out of 140 subjects on these medications (31.4%) said the product was appropriate to use. As shown in the Appendix (Table A4, Response to FDA Question), in the LDL arm there were 220 women too young in the SA population of 391 women (56.3%), and 29 out of the 220 women (13.2%) who were too young responded SA=Yes. There were 101 women who responded SA=Yes, so of the women who responded SA=Yes, 29/101 (28.7%) were too young.

The proportions of subjects who selected SA=Yes without knowing required cholesterol numbers was similar in the two arms, although in the total SA populations there were significantly more subjects who did not know their LDL-C than those who did not know their Total-C. In the LDL-C arm, 268/714 (37.5%) did not know their LDL-C, but of these only 60/268 (22.4%) selected SA=Yes. In the Total-C arm, 149/708 (21%) did not know their Total-C, but of these 26/149 (17.4%) selected SA=Yes.

The Sponsor determined the Framingham coronary heart disease (CHD) risk for subjects who selected SA=Yes (Table 13 and Table 14). Men who selected SA=Yes tended to have higher CHD risk than the women. About 40-55% of the men with SA=Yes fell in the 5% to 20% CHD risk range compared with approximately 25% of the women falling in this range. About 11% of men with SA=Yes had <5% CHD risk, but over 40% of the women with SA=Yes had <5% CHD risk. About one third of subjects (men and women combined) who said SA=Yes in the LDL-C arm, and about 43% in the Total-C arm, had Framingham CHD risk of 5% to 20%. The SELECT label was designed to target the CHD risk range of 5%-20% for OTC Mevacor use in individuals who have two or more risk factors. The LDL-C label criteria are similar to, but not precisely the same as, NCEP ATP III guidelines. For individuals who have a 10-year risk < 10%, ATP III guidelines recommend consideration of drug therapy when LDL levels are $\geq$160 mg/dL with two or more risk factors (see Table 2).

The Sponsor investigated the reasons why subjects chose SA=Yes or PD=Yes incorrectly. The most frequent reasons for choosing SA=Yes, when the subject was already taking lipid-lowering medication, were to replace the prescription medication or specifically to replace it because of lower cost. The Sponsor also examined the reasons why subjects were interested in exploring non-prescription medicine rather than prescription medicine for cholesterol. The most frequent reasons cited by those with SA=Yes were less expensive (50%), convenience (29%), don't have to see the doctor (15%), and feels safer/less side effects (11.3%).

Participants who had decided PD=Yes but who reported that they were already taking a lipid-lowering medication were asked if they planned to take the OTC Mevacor along with the prescription medicine or in place of it. About half responded that they would replace their prescription medication, but about 30% said they would take Mevacor along with it. Of the latter subjects, about one quarter said they would talk to a doctor.

On average, about 30% of participants with heart disease, stroke, or diabetes wanted to purchase the product. About two thirds of these subjects were not taking any lipid-lowering medications.

There were only four participants in the total study population stated that they were pregnant and one participant who was breastfeeding. All of these individuals made acceptable decisions. Twenty-two females stated that they may become pregnant. Of these participants, none of them decided to purchase the product. However, two participants stated that they were appropriate for the product. The sponsor mitigated both subjects on the basis of their open-ended responses. This reviewer disagrees with one of these mitigations, and the other is debatable. The samples of pregnant women and women who say they may become pregnant were small, but the procedure of asking a women if she "thinks she may become pregnant" may underestimate the potential for use by pregnant women, since many pregnancies are unintended.

In the SELECT study, there were 39/1495 (2.6%) in SA population, and 39/1494 (2.6%) participants in the PD population, with liver disease or liver problems. Of these participants, three (7.7%) responded SA=Yes, and 3 (7.7%) responded PD=Yes. SELECT also enrolled subjects were who were on potentially interacting medications. Specifically, 21/1493 (1.4%) of the participants evaluated for SA, and 21/1494 (1.4%) of the participants evaluated for PD, were taking potentially interacting medication. Four (19.1%) of the participants who were taking interacting medication responded SA=Yes, and three (14.3%) of them said PD=Yes. Of these 4 participants who responded SA=Yes, all stated they would talk to their doctor as did 2 who responded PD=Yes.

The SELECT study did not evaluate some issues pertinent to effective consumer use of OTC statins for primary prevention of CV events. Namely, consumers must understand that continued monitoring of serum lipid profiles is required and that the drug therapy must in most cases be continued for life. Moreover, treatment goals may need to be modified as new health conditions arise. There is only one line in a lengthy Drug Facts label that states "If you stop taking this product your cholesterol will go back up". SELECT also did not evaluate how consistently consumers will get follow up cholesterol testing to see if they are reaching their treatment goal. These issues were assessed in the CUSTOM actual use study in the previous submission of NDA 21-213, however the labels differed in their handling of these issues.

1.3.3 Safety

No safety data were acquired in SELECT except for adverse events that may have occurred while lab specimens were taken for the lipid profiles.

1.3.4 Dosing Regimen and Administration

The proposed dosing for Mevacor Daily is one 20 mg tablet daily with the evening meal.

1.3.5 Drug-Drug Interactions

Several drugs (cyclosporine, clarithromycin, itraconazole, ketoconazole, nefazodone, erythromycin, and HIV protease inhibitors) have the potential to interact with lovastatin when administered concomitantly. These drugs and grapefruit juice, are strong CYP3A4 inhibitors, and may increase plasma HMG-CoA inhibitory activity levels, and therefore may increase the individual's risk of myopathy.

The risk of myopathy is also increased by the drugs gemfibrozil, other fibrates, and niacin (nicotinic acid). These are not potent CYP3A4 inhibitors, but can cause myopathy when given alone.

Table 1 lists prescription labeling recommendations for interacting agents for Mevacor:

Table 1. Summary of Drug Interactions from Prescription Labeling

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis	
Interacting Agents	**Prescribing Recommendations**
Itraconazole Ketoconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone	Avoid lovastatin
Gemfibrozil Other fibrates Lipid-lowering doses (>/=1 g/day) of niacin Cyclosporine Danazol	Do not exceed 20 mg lovastatin daily
Amiodarone Verapamil	Do not exceed 40 mg lovastatin daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

1.3.6 Special Populations

Use of Mevacor is contraindicated if breastfeeding or pregnant. Prescription labeling states that cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of HMG-CoA reductase inhibitors such as MEVACOR to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR is contraindicated during pregnancy and in nursing mothers. **MEVACOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If the patient becomes pregnant while taking this drug, MEVACOR should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus. Use of Mevacor is also contraindicated in the presence of active liver disease or unexplained persistent elevations of serum transaminases, or rhabdomyolysis.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Mevacor (lovastatin) is a cholesterol-lowering agent isolated from a strain of Aspergillus terreus. After oral ingestion, lovastatin, which is an inactive lactone, is hydrolyzed to the corresponding (beta)-hydroxyacid form, which is the principal metabolite. This is an inhibitor of 3- hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate limiting step in the biosynthesis of cholesterol.

In the LDL-C paradigm, the sponsor proposes to market MEVACOR™ Daily to men 45 years and older and women 55 years of age and older, with LDL-C level between 130 mg/dL and 170 mg/dL, and one or more additional risk factors for CHD. In the Total-C paradigm, the target population is also men 45 years and older and women 55 years of age and older, but with Total-C level between 200 mg/dL and 240 mg/dL, and one or more additional risk factors for CHD (women only, but women also need HDL under 60 mg/dL). Men in the Total-C paradigm need to meet only age and Total-C criteria.

2.2 Currently Available Treatment for Indications

There are no OTC drugs currently available for the treatment of hypercholesterolemia in the United States. Simvastatin is available behind the counter in the U.K. Current medical practice is such, that elevated serum cholesterol is treated based on the latest National Cholesterol Education Program (NCEP) Adult Panel Treatment Panel (ATP) III guidelines. (Table **2**, References 1 and 2).

According to the ATP III guidelines, elevated LDL cholesterol is the primary target of cholesterol-lowering therapy. Therapeutic lifestyle changes form the foundation of clinical primary prevention, and include attention to diet, increased physical activity and weight control to reduce CHD risk. However, some people at higher risk because of high LDL or because of multiple risk factors are candidates for lipid lowering therapy. The clinical approach intensifies preventive strategies for higher-risk persons. LDL goals depend on a person's absolute risk for CHD—the higher the risk, the lower the goal.

The ATP III guidelines (see Table 2) recognize three CV risk categories for which treatment approaches and goals of therapy are defined. The risk categories estimate an individual's risk of experiencing a CV event over a 10-year period. In addition to specific CV risk factors listed below, ATP III uses Framingham point scores in estimating the 10-year CHD risks, where age, sex, total-C, smoking status, HDL-C, systolic blood pressure and hypertension treatment status determine the 10-yr risk. The CHD risk factor counts and the Framingham 10-yr risk estimates together determine whether an individual falls into one of three categories:

- **[High Risk Category]** CHD or CHD risk equivalents (10-yr risk > 20%)

- [**Moderate Risk Category**] Two or more CHD risk factors, divided into sub-categories of moderately high 10-yr risk (10-20%) and moderate 10-yr risk < 10%.
- [**Lower Risk Category**] Zero or one CHD risk factor

The moderate risk category is divided into two sub-categories according to Framingham 10-yr risk.

The CHD risk equivalents for the High Risk Category are defined as follows. Individuals with diabetes but without clinically evident CHD, those with other clinical forms of atherosclerotic disease (e.g., peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease), and those with multiple risk factors that confer a 10- year risk for CHD>20%. These CHD risk equivalent categories carry a risk for major coronary events equal to that of established CHD, ie, > 20% per 10 years (ie, more than 20 of 100 such individuals will develop CHD or have a recurrent CHD event within 10 years).

The CHD risk factors include:

- family history of premature coronary heart disease (below age of 55 years in a male parent or sibling or below 65 in female relative)
- hypertension (BP > 140/90 mmHg or an antihypertensive medication)
- cigarette smoking
- diabetes mellitus
- low high density lipoprotein cholesterol (HDL-C) (< 40 mg/dL), and
- age (men > 45 years, women > 55 years).

HDL-C > 60 mg/dl is a negative risk factor, i.e., one other factor can be negated by a high HDLC level.

Table 2. Summary of NCEP ATP III Guidelines for the Treatment of High Blood Cholesterol: LDL Goals and Criteria for Therapeutic Lifestyle Changes (TLC) and Drug Therapy[1,2]

Risk Category	LDL Goal (mg/dL)	LDL Level at which to initiate TLC (mg/dL)	LDL level at which to consider Drug Therapy (mg/dL)
CHD or CHD risk equivalents (10-yr risk > 20%)	< 100	≥ 100	≥ 100 (if <100, consider drug options)*
2+ risk factors (10-yr risk 10-20%)	< 130**	≥ 130	≥ 130 (if 100-129, consider drug options)**
2+ risk factors (10-yr risk <10%)	< 130	≥ 130	≥ 160
0 – 1 risk factor (10-yr risk < 10%)#	160	≥ 160	≥ 190 (if 160-189, drug therapy optional)

* for those at very high risk for a CV event, 2004 recommendations have an option for more aggressive treatment with an LDL-lowering goal of < 70 mg/dL with consideration of drug treatment for LDL levels of ≥100

** for moderately high-risk persons, the 2004 ATP III Update has as a therapeutic option to set the treatment goal at an LDL < 100 mg/dL and to use drug treatment if LDL is 100-129 mg/dL,

\# almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary

In the ATP III Guidelines for treatment of high blood cholesterol as summarized in Table **2**, the Therapeutic Lifestyle Changes (TLC) are diet, weight management and exercise. Highlighted in yellow are the groups targeted by the Mevacor Daily label. (Background Memo Dr. Parks, Jan 2005 Advisory Committee Meeting)

The NCEP ATP-III Guidelines also identified other lipid parameters beyond LDL-C that require treatment intervention if abnormal. Specifically, the optimal level serum triglyceride (TG) levels are < 150 mg/dL. In patients who have reached their LDL-C goal but whose TGs were > 200 mg/dL, a secondary target of therapy is non-HDL-C (defined as total cholesterol minus HDL cholesterol) with the goal being set 30 mg/dL higher than that for LDL-C. In many instances, this secondary target of therapy must be addressed with additional lipid lowering therapies (e.g., fibrates, niacin). Table 3 summarizes LDL-C and non-HDL-C goals of therapy by risk category.

Table 3. LDL and non-HDL Goals of Therapy

Risk Category	LDL Goal (mg/dL)	Non-HDL Goal (mg/dL)
CHD and CHD risk equivalent (10-yr risk > 20%)	< 100	< 130
2+ risk factors (10-yr risk ≤ 20%)	< 130	< 160
0-1 risk factor	< 160	< 190

In July 2004, members of the Coordinating Committee of the National Cholesterol Education Program published updates to NCEP ATP-III. These revised recommendations stated that in individuals with very high risk for a CV event, an LDL-C goal of < 70 mg/dL is a therapeutic option. In addition, for moderately high-risk patients (individuals with 2 or more CHD risk factors together with a 10-20% risk for a heart attack within 10 years, the overall goal is still an LDL less than 130 mg/dL. There is a therapeutic option to set the treatment goal at an LDL less than 100 mg/dL, and to use drug treatment if LDL is 100-129mg/dL.

MO Comment: *The MEVACOR™ Daily label targets consumers in the risk groups corresponding to the highlighted rows in* Table 2. *However, the MEVACOR™ Daily label directions (copies of the labels are in Section 10.2) are not entirely consistent with ATP III Guidelines since it is not practical to have consumers actually calculate their Framingham 10-year coronary heart disease risk score. The following are some examples of discrepancies. First, there are the consumers for whom ATP III does not recommend drug therapy but for whom the label says the product "is right for you". For example, in the case of a female of age 55, LDL 130 mg/dL and total cholesterol 210 mg/dL, with systolic BP 130 on medication, the Framingham 10 yr risk is 4% (if HDL is 55 mg/dL) and ATP III would not recommend drug treatment; but such a subject qualifies under the LDL label paradigm. As another example for the Total-C paradigm, a 45 year-old male with cholesterol 200-239 mg/dL has Framingham 10 yr risk of 4% and would generally not be treated unless the LDL were greater than 190 mg/dL, but such a subject would qualify to use the drug.*

In addition to the low CHD subjects for which the labels and the ATP III guidelines are not completely consistent, there are high CHD risk subjects who are also allowed to use the product according to label criteria, but who should be treated by a physician. For example, a male, age 55, with LDL 170 and Total C 250, hypertensive (140/90 treated) with a history of smoking, qualifies by label despite a Framingham score 17 and risk >30% (if the HDL is 40). Hence the label criteria allow some consumers with high CHD risk who ought to be receiving care from a physician to use the product, as well as consumers at lower risk who do not require treatment according to ATP III.

Also not specifically related to ATP III guidelines, there are other issues that concern whether consumers will use OTC statins effectively for primary prevention of CV events. Namely, they must understand that continued monitoring of serum lipid profiles is required and that the drug therapy must in most cases be continued for life. Moreover, treatment goals may need to be modified as new health conditions arise. There is only one line in a lengthy Drug Facts label that states "If you stop taking this product your cholesterol will go back up". It is also not clear how consumers will get follow up cholesterol testing to see if they are reaching their treatment goal.

2.3 Availability of Proposed Active Ingredient in the United States

There are several HMG-CoA reductase inhibitors available as prescription drugs for the treatment of elevated serum cholesterol in the United States. This class of drugs is not currently approved for over-the-counter marketing.

2.4 Important Issues With Pharmacologically Related Products

There are several important safety issues with HMG-CoA reductase inhibitors with respect to over-the-counter marketing, as listed in prescription labeling:

- **Myopathy/rhabdomyolysis**. Lovastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10× the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related.

- **Pregnancy Category X**. Safety in pregnant women has not been established. Lovastatin has been shown to produce skeletal malformations in offspring of pregnant mice and rats dosed during gestation at 80 mg/kg/day. Female rats dosed before mating through gestation at 80 mg/kg/day also had fetuses with skeletal malformations. The 80 mg/kg/day dose in mice is 7 times the human dose based on body surface area and in rats results in 5 times the human exposure based on AUC. In pregnant rats given doses of 2, 20, or 200 mg/kg/day and treated through lactation, the following effects were observed: neonatal mortality (4.1%, 3.5%, and 46%, respectively, compared to 0.6% in the control group), decreased pup body weights throughout lactation (up to 5%, 8%, and 38%, respectively, below control), supernumerary ribs in dead pups (affected fetuses/total: 0/7,

1/17, and 11/79, respectively, compared to 0/5 in the control group), delays in ossification in dead pups (affected fetuses/total: 0/7, 0/17, and 1/79, respectively, compared to 0/5 in the control group) and delays in pup development (delays in the appearance of an auditory startle response at 200 mg/kg/day and free-fall righting reflexes at 20 and 200 mg/kg/day).

Direct dosing of neonatal rats by subcutaneous injection with 10 mg/kg/day of the open hydroxyacid form of lovastatin resulted in delayed passive avoidance learning in female rats (mean of 8.3 trials to criterion, compared to 7.3 and 6.4 in untreated and vehicle-treated controls; no effects on retention 1 week later) at exposures 4 times the human systemic exposure at 80 mg/day based on AUC. No effect was seen in male rats. No evidence of malformations was observed when pregnant rabbits were given 5 mg/kg/day (doses equivalent to a human dose of 80 mg/day based on body surface area) or a maternally toxic dose of 15 mg/kg/day (3 times the human dose of 80 mg/day based on body surface area).

Rare clinical reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. However, in an analysis of greater than 200 prospectively followed pregnancies exposed during the first trimester to MEVACOR or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the general population. This number of pregnancies was sufficient to exclude a 3-fold or greater increase in congenital anomalies over the background incidence.

Maternal treatment with MEVACOR may reduce the fetal levels of mevalonate, which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering drugs during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolemia. For these reasons, mevacor should not be used in women who are pregnant, or can become pregnant. MEVACOR should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. Treatment should be immediately discontinued as soon as pregnancy is recognized.

- **Hepatic Effects**. The most common statin-induced hepatic effect is a self-limited, asymptomatic, reversible, dose-related elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST). There are rare reports of acute liver failure associated with all statins. Persistent increases to more than 3 times the upper limit of normal occurred in serum transaminases in 1.9% of adult patients who received lovastatin for at least one year in early clinical trials. When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin and were not associated with jaundice or other clinical signs or symptoms. In the EXCEL study of lovastatin, the incidence of persistent increases in serum transaminases over 48 weeks was 0.1% for placebo, 0.1% at 20 mg/day, 0.9% at 40 mg/day, and 1.5% at 80 mg/day in patients. However, in post-marketing experience with MEVACOR, symptomatic liver disease has been reported rarely at all dosages.

  In Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), the number of participants with consecutive elevations (to > 3 times the upper limit of normal) of either ALT or AST, over a median of 5.1 years of follow-up, was not

significantly different between the MEVACOR and placebo groups (18 [0.6%] vs. 11 [0.3%]). The starting dose of MEVACOR was 20 mg/day; 50% of the MEVACOR treated participants were titrated to 40 mg/day at Week 18. Of the 18 participants on MEVACOR with consecutive elevations of either ALT or AST, 11 (0.7%) elevations occurred in participants taking 20 mg/day, while 7 (0.4%) elevations occurred in participants titrated to 40 mg/day. Elevated transaminases resulted in discontinuation of 6 (0.2%) participants from therapy in the MEVACOR group (n=3,304) and 4 (0.1%) in the placebo group (n=3,301).

It is recommended that liver function tests be performed prior to initiation of therapy in patients with a history of liver disease, or when otherwise clinically indicated. It is recommended that liver function tests be performed in all patients prior to use of 40 mg or more daily and thereafter when clinically indicated. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation for confirmation and be followed thereafter with frequent liver function tests until these abnormality(ies) returns to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist, withdrawal of therapy with MEVACOR is recommended.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than three times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR. These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

MO Comment: *As of the date of this review, the labeling for LFT monitoring is as stated above. Additional data to assess hepatic risk with the use of lovastatin in patients with asymptomatic liver disease was included in this resubmission and is under review by the Division of Metabolic and Endocrine Products (DMEP) and the Division of Drug Risk Evaluation (DDRE). See DMEP and DDRE reviews.*

- **Drug interactions**. Relative contraindications exist in patients taking specific concomitant medications (cyclosporine, gemfibrozil, other fibrates, niacin, macrolide antibiotics, various anti-fungal agents, and cytochrome P-450 inhibitors).

2.5 Presubmission Regulatory Activity

The initial NDA 21-213 was submitted to FDA in 1999. The Agency sent the Sponsor a non-approval letter for NDA 21-213, OTC lovastatin, in October, 2000. Eight specific items were identified as clinical efficacy and safety deficiencies:

- Current National Cholesterol Education Program (NCEP) Guidelines were not incorporated in the OTC treatment paradigm
- Inadequate information was provided, specifically regarding the Mevacor 10 mg dose and the proposed OTC target population, to support an expectation of a clinical benefit for

Mevacor based on extrapolation from the clinical outcomes study, Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)

- The OTC study program had not included a cholesterol treatment goal, did not evaluate whether consumers would comprehend the importance of a treatment goal, and did not address whether consumers would make appropriate decisions in the event of not achieving that treatment goal
- The clinical and actual use studies failed to demonstrate that consumers understood the complexities of treating a chronic medical condition such as hypercholesterolemia. Specifically, assessment of individual CV risk, compliance, and adherence to chronic lovastatin therapy were deficiencies noted in the review of these trials.
- The program did not explain how a consumer can use an over-the-counter product whose prescription label recommends hepatic transaminase monitoring. In addition, the program did not demonstrate an ability of consumers to comprehend the risk of serious muscle toxicity associated with Mevacor therapy.
- Lovastatin is extensively metabolized by cytochrome P450 3A4, and many drugs may interfere with the metabolism of Mevacor OTC, which would increase the risk for serious muscle toxicity. The OTC program did not demonstrate that consumers would understand the importance of drug-drug interactions.
- Post-approval consumer education programs and materials were not adequately tested. Information on the availability of accurate cholesterol testing in the OTC setting to allow informed selection and monitoring of therapy by consumers was not adequately provided in the NDA.
- Lovastatin is labeled Pregnancy Category X (not to be used in pregnancy). Given that Mevacor OTC was likewise proposed to be contraindicated in pregnancy, label comprehension in this regard as well as the actual potential of such use was not assessed. Additional postnatal development studies in animals (modeling human fetal neurological development) were recommended to shed further light on risks to the fetus of in utero lovastatin exposure

The Sponsor's first resubmission in 2004 to NDA 21-213 included a clinical development program that addressed many of the deficiencies in the October 2000 non-approval letter. The resubmission included an actual use study, "A Consumer Use Study of Over-The-Counter MEVACOR [CUSTOM]". As reviewed by Dr. Parks (TL memo), the resubmission showed that overall this product, at the proposed dose, is safe and effective for the targeted population. Safety concerns that needed to be further addressed include the safety of the product in patients with asymptomatic liver disease and consumer comprehension of a label that better advises against use in women of childbearing potential. The principal deficiency for the resubmission remained poor consumer comprehension of the management of hypercholesterolemia. A Joint Session of the Nonprescription Drugs Advisory Committee with the Endocrine And Metabolic Drugs Advisory Committee was held on January 13-14, 2005. At that meeting, the applicant maintained that although a large percentage of consumers failed to select the product based on all eligibility criteria, the majority of purchasers made an appropriate decision based on physician advice. As stated by the applicant at the meeting, 57% of purchasers relied on physician advice to select the

product. These results demonstrated the inability of consumers, on their own, to make decisions on the appropriateness of statin therapy.

On 2/23/05 the Agency sent a non-approval letter that stated that the results of the label comprehension and actual-use studies demonstrated that, as a whole, consumers did not correctly self-select use of the product based on the labeled criteria and identified remaining areas of concern for NDA 21-213. The letter stated that to pursue OTC Mevacor further, the Sponsor should perform a further self-selection/use study or studies to demonstrate that consumers can make decisions to use the product with an understanding of their likelihood of benefits versus risks. Specific items requested were:

- A **self-selection use study**, with a suggestion to compare the new label against the label used in the Custom Study, and with request for justification for any deviation from the Drug Facts labeling format requirements.
- Improved compliance with the muscle pain warning. In the Custom Study, **only 75% of subjects who developed muscle pain made a correct decision about use of Mevacor OTC. Serious muscle toxicity is perhaps the greatest risk of toxicity for consumers using this product.** Labeling would need to be developed that accomplished a demonstrably higher rate of compliance with this important warning. Label comprehension testing should document the improvement in this labeling.
- An improved label that yields adequate consumer understanding of the risks of drug exposure during pregnancy. Testing of consumer comprehension and consumer self-selection **must show that the label** for nonprescription lovastatin **adequately discourages purchase and use of this product by women of childbearing potential**.
- A simpler label that conveys benefit with long-term use for the labeled population (based on eligibility criteria), and the likelihood of lesser a benefit if the criteria are not met (including a lower benefit than if the patient is properly treated for those with high baseline LDL-C or who inadequately respond to the Mevacor dose), and risks for serious adverse events.
- Information from the Sponsor's proposed Mevacor OTC Statin Self-Management System which is essential to assist the consumer in making decisions on use of the product would need to be provided in the resubmission, and would need to be mandated as a condition of approval. Other information which is disseminated that encourages correct selection and use of the product is left up to the Sponsor, but these mechanisms cannot be essential to use if they cannot be mandated as a condition of approval. The Sponsor was encouraged to convey eligibility and benefit information on the principal display panel of the Mevacor OTC package and all ancillary labeling (e.g. shelf talkers, brochures). The Sponsor was asked whether the label eligibility criteria will be a part of all advertising.
- **Sufficient evidence that the risk of hepatotoxicity is minimal** in patients with common asymptomatic liver diseases in order to support removal of the current recommendation to monitor hepatic transaminases. Alternatively, the Sponsor needed to provide sufficient evidence that consumers can make clinical safety assessments of hepatic risks before initiating therapy with nonprescription lovastatin.

The non-approval letter stated that the actual use study data in the resubmission suggested that most, but not all, subjects made satisfactory decisions with regard to the use of the product (after

self-selection). This was seen from the percentage of USERS who had their LDL-cholesterol checked (about 70%) and the percentage who made a correct decision on whether to continue use of the product (about 75%). Whether these percentages would still apply in the consumer environment where cholesterol testing is not readily available was not clear.

At an April 25, 2005 meeting with the Sponsor, the Agency confirmed that the treatment paradigm must be consistent with NCEP ATP III Guidelines which use LDL-cholesterol as the basis for determining the need for cholesterol lowering treatment. The Sponsor had proposed an alternative treatment paradigm based upon Total-C, and the SELECT study tested and compared labels for both treatment paradigms.

2.6 Other Relevant Background Information

The only country where statins are available without a prescription is the United Kingdom. Simvastatin (Zocor Heart Pro) 10 mg tablets were reclassified from prescription to over-the-counter status (for sale in pharmacies) in May, 2004. Simvastatin 10 mg is indicated for men 45 years and over and women 55 years and over with one or more risk factors for CHD.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

NA

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

In support of the current resubmission, the sponsor provided results of two label comprehension studies, a self-selection study, and a safety update which included the final report, “Study Of Potential Hepatotoxicity Of Lovastatin In The Northern California Kaiser Permanente Liver-Disease Population”. Label comprehension studies evaluate how well drug labels are understood by the consumer. Self-selection studies determine whether a consumer, by examining the product label, can make an correct assessment as to whether or not he or she can use the product. The label comprehension studies are under review by Laura Shay, RN, MS, C-ANP in the Division of Nonprescription Clinical Evaluation. The hepatic study and safety update are being reviewed by Dr. Eileen Craig of the Division of Endocrine and Metabolic Drug products. The SELECT self-selection study is reviewed in this document.

4.2 Table of Consumer Studies

STUDY NUMBER	STUDY TITLE
P087	MEVACOR™ OTC PIVOTAL SELECT LABEL COMPREHENSION STUDY
P088	MEVACOR™ OTC MUSCLE WARNING COMPREHENSION STUDY
P086	SELF EVALUATION OF LOVASTATIN TO ENHANCE CHOLESTEROL TREATMENT (SELECT)

4.3 Review Strategy

This review covers the results of the Self Evaluation of Lovastatin to Enhance Cholesterol Treatment (SELECT) Study (P086). The study is not a placebo controlled efficacy and safety trial, but is a self-selection study which evaluates the correctness of consumers' decisions whether a medication is appropriate for them to use. Therefore, this review does not follow the headings of the CDER Clinical Review Template. The study design, methodology, consumer behavior and drug use data will be reviewed in the efficacy part of the template.

The study description (design, methodology, and results) in an abbreviated form were taken from the sponsor's submission of the NDA. Most of the reviewer's comments are written in italic font. The tables unless otherwise specified are reproduced from the sponsor's study report.

4.4 Data Quality and Integrity

The Quality Control and Quality Assurance measures were followed as dictated by the appropriate department's Standard Operating Procedures.

4.5 Compliance with Good Clinical Practices

The Sponsor stated that this study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

4.6 Financial Disclosures

Form FDA 3454 was not submitted. The sponsor was previously informed that this was not necessary since no drug was dispensed.

5 CLINICAL PHARMACOLOGY

NA

6 INTEGRATED REVIEW OF EFFICACY

This section reviews Study P086, Self Evaluation of Lovastatin to Enhance Cholesterol Treatment (SELECT). This was a multi-center consumer self-selection study, performed from 24 Oct 2006 through 23 Dec 2006, to observe, record, and query participants' self-assessment and purchase decisions, using scripted interviews. No drug was dispensed. Cholesterol testing was made available to subjects who requested it prior to making their selection decision. All subjects had cholesterol testing and blood pressure measurement at the end of the study procedure, if they had not requested cholesterol testing earlier.

A significant portion of the efficacy data for nonprescription lovastatin relied on 2 controlled studies: the Expanded Clinical Experience with Lovastatin (EXCEL) and Air Force/Texas Coronary Atherosclerosis Project (AFCAPS/TexCAPS). These studies were submitted and reviewed as efficacy supplements to the prescription NDA, and summaries are included in prescription labeling. See Dr. Parks Background Memo for the January 13 and 14th 2005 Advisory Committee Meeting for discussion of efficacy results from these two studies.

6.1 Indication

As stated in the *Use* section of the MEVACOR™ Daily label, the indication is "To help lower cholesterol, which may prevent a first heart attack". The label in the SELECT study is modified from that for the previous review cycle, for which the actual use study, "A Consumer Use Study of Over-the-Counter MEVACOR" (CUSTOM) was submitted.

CUSTOM was an open-label, long-term actual use study to observe consumer self-selection and de-selection behavior in a naturalistic OTC setting. In the CUSTOM study, 11,252 individuals responded to advertising. Of these, 3,316 individuals evaluated MEVACOR™ OTC at the study sites. Fifty-nine percent of the evaluators were men. The median age was 53 years, 28% were non-Caucasian, and 12% were low literate. Participants were asked to make a self-selection decision. They were able to purchase 1 to 4 cartons (45-day supply per carton) of the study drug. Participants' behavior was recorded over the treatment period, which had a maximum duration of 26 weeks, for appropriateness when compared to directions on the package label.

As summarized by the Sponsor, the Agency non-approval letter of Feb 23, 2005 identified the following deficiencies in CUSTOM:

- **Women <55 years of age.** In CUSTOM, of the women <55 years of age who evaluated the product, 23.5% (161/685) elected to use MEVACOR™ OTC. In CUSTOM 37% (161/430) of the female User population were women <55 years of age.
- **Women of childbearing potential.** Since women <55 years of age who used MEVACOR™ OTC in CUSTOM were not asked if they were menopausal, it was assumed that they were capable of conceiving a child. A question regarding childbearing potential was not asked in CUSTOM and there was no warning on the label; however, the label did contain a warning against use in pregnancy.

- **Low CHD risk users (<5% risk of CHD in 10 years).** In CUSTOM, 27.3% (289/1059) of the users were considered low risk based on personal characteristics as defined by the Framingham Risk Calculator.

The present application includes a consumer self-selection study called "Self Evaluation of Lovastatin to Enhance Cholesterol Treatment (SELECT). The Sponsor designed the SELECT study to address these deficiencies of CUSTOM.

SELECT STUDY

The SELECT study investigated the impact of new, simplified labels (LDL-C and Total-C) on participants' self-assessment and purchase decisions, and it collected data to investigate why participants made inconsistent or inappropriate decisions.

The SELECT study tested participants' ability to make self-selection decisions with the outer carton label only. After reading the label, they decided if the product was appropriate for their use and if they would like to buy it. The study was designed to simulate the self-selection process. A detailed questionnaire was used to understand behaviors associated with self-assessment and purchase decisions that are not consistent with the label directions. There was specific focus on the following areas targeted for improvement:

- Decrease the proportion of women <55 years of age among purchaser population.
- Decrease the proportion of women of childbearing potential among purchaser population.
- Decrease the proportion of low CHD risk (<5% risk of CHD in 10 years) among purchasers.

The key elements of the CUSTOM and the SELECT LDL-C labels are compared in Table 4 (copies of the proposed SELECT and CUSTOM labels are provided in Section 10.2*)*. There are two versions of the SELECT label which were tested in the two arms of the SELECT study. They are called the "LDL-C Paradigm" and the "Total-C Paradigm", which have different eligibility criteria for use, the former based on LDL-C and the latter based on Total-C. The two SELECT labels are compared in Table 5.

Table 4. Comparison of CUSTOM and SELECT Labels (not exact wording of labels)

CUSTOM Label†	SELECT LDL-C paradigm Label†
	Three NEW sections outside of Drug Facts to guide consumers: Front panel – color coded age guidance by gender Back panel – lists 3 criteria that should be met before buying • tried a healthy diet and exercise • had a fasting cholesterol test and know your numbers • LDL-C must be 130-170 Inside panel – a flow chart to assist consumers determine if this product is right for them. Also provides information and direction if one does not meet any specific criteria. Consumers are told that if they do not meet specific criteria they might be lower CHD risk and will have reduced benefit or at higher risk and need a stronger medicine.
Warnings	
"Do not use if you" ➢ Have liver disease *(Moved to Ask your Doctor before use)* ➢ Know you are allergic to lovastatin ➢ Are pregnant or breast feeding ➢ Have previous muscle pain from cholesterol lowering medication *(Deleted from label)*	"Do not use if you" ➢ know you are allergic to lovastatin ➢ Are pregnant or breast feeding ➢ Think you may become pregnant *(New expanded Warning)*

CUSTOM Label†	SELECT LDL-C paradigm Label†
Warnings (Cont.)	
"Talk to doctor or pharmacist before use if you are taking" ➢ Any Prescription Medicines *(Enhanced by listing treatment categories, including cholesterol medicines, and added large quantities of grapefruit juice)* ➢ Cholesterol lowering medicines *(Moved to "Ask your doctor before use and modified to prescription cholesterol medicines)* ➢ New Prescriptions *(Moved to its own section " When using this product …if there is a change in your health")*	"Ask a doctor or pharmacist before use if you are taking" ➢ Prescription medicines specified by treatment category, including any cholesterol medicines ➢ Large quantities of grapefruit juice (≥ 1 qt/day) ➢ unsure of your cholesterol numbers or have not had a fasting cholesterol test within the last year
"Do not use unless directed by a doctor if you have " *(These factors were changed to "Ask you doctor before use")* ➢ Heart disease ➢ Stroke ➢ Diabetes ➢ LDL-C >170 mg/dL ➢ Triglycerides ≥200 mg/dL *(Deleted from label)* ➢ HDL ≥ 60 mg/dL *(Now specific to women)*	"Ask your doctor before use" ➢ Taking prescription cholesterol medicine ➢ LDL-C >170 mg/dL ➢ Women < 55, Man <45 ➢ Woman with HDL ≥ 60 mg/dL ➢ Liver Disease ➢ Heart disease ➢ Stroke ➢ Diabetes
"During use talk to a doctor if you" ➢ Develop unexplained muscle pain ➢ New medical condition ➢ New prescription	"When using this product, talk to a doctor if there is a" ➢ Change in health ➢ New medical condition ➢ New prescription "Stop use and ask a doctor ➢ if you develop any unexplained muscle pain, weakness or tenderness.

MO Comment: *The graphical layout of the CUSTOM label was densely packed and presented a complex algorithm to determine eligibility for use. The SELECT label uses a set of flowchart graphics to make the self-selection algorithm easier to follow (see Section 10.2 for reproductions of the proposed label). The SELECT label places a greater emphasis on the appropriate age for which women and men should use this product.*

Table 5. Comparison of SELECT labels, LDL-C and Total-C (not exact wording on labels)

LDL-C paradigm Label†	Total-C paradigm Label‡
Three NEW sections outside of Drug Facts to guide consumers: 1. Front panel – color coded age guidance by gender 2. Back panel – lists 3 criteria that should be met before buying • tried a healthy diet and exercise • had a fasting cholesterol test and know your numbers • LDL-C must be 130-170 3. Inside panel – a flow chart to assist consumers determine if this product is right for them. Also provides information and direction if one does not meet any specific criteria. Consumers are told that if they do not meet specific criteria they might be lower CHD risk and will have reduced benefit or at higher risk and need a stronger medicine.	Note: Total Cholesterol 200 to 240 is substituted for LDL-C 130-170 throughout the Label 2. Back panel – lists 4 criteria that should be met before buying • tried a healthy diet and exercise • had a fasting cholesterol test and know your numbers • Total cholesterol must be 200 to 240 • Women must also have HDL "good cholesterol 1 to 59 3. Inside panel – flow chart - splits into separate flows for Men and Women after knowing your Total Cholesterol. Women are required to have HDL <60 and have an additional Heart Disease Factor. Neither criteria is required for Men.
Warnings	
"Do not use if you" ➢ know you are allergic to lovastatin ➢ Are pregnant or breast feeding ➢ Think you may become pregnant *(New expanded Warning)* "Ask a doctor or pharmacist before use if you are taking" ➢ Prescription medicines specified by treatment category, including any cholesterol medicines ➢ Large quantities of grapefruit juice ➢ unsure of your cholesterol numbers or have not had a fasting cholesterol test within the last year "Ask your doctor before use" ➢ Taking prescription cholesterol medicine ➢ LDL >170 mg/dL ➢ Women < 55, Man <45 ➢ Woman with HDL ≥ 60 mg/dL ➢ Liver Disease ➢ Heart disease ➢ Stroke ➢ Diabetes	"Ask your doctor before use" ➢ Total > 240 mg/dL

MO Comment: *The Total-C label is intrinsically more complex because the flowchart algorithm is divided into separate paths for men and women, whereas men and women are treated the same in the LDL-C paradigm. This added complexity may be balanced against the greater familiarity of total cholesterol versus LDL cholesterol in the general population, and simplified criteria for men to qualify for drug use. The results of the SELECT study found that the two label paradigms performed similarly overall in terms of correct self-selection. In* Table 5*, the last entry in the right column was corrected from the submission to read " Ask your doctor before use ►Total > 240 mg/dL.*

6.1.1 Methods

The remainder of Section 6 will focus on the self-selection study entitled "Self Evaluation Of Lovastatin To Enhance Cholesterol Treatment" (SELECT).

Study Design
This was an "all-comers," two-arm, multi-center, non-drug, self-selection study, conducted to study the self-assessment and purchase decisions of OTC consumers. Two revised product labels were used, which were designed to minimize the proportion of women <55 years of age among the purchaser population, minimize the proportion of women of childbearing potential among the purchaser population, and minimize the proportion of low-CHD risk purchasers. The study evaluated participants' understanding of eligibility criteria using two different label paradigms, one for each study arm. One label paradigm required users to have LDL cholesterol 130 to 170 mg/dL, based on National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) Guidelines for lipid lowering therapy, which are used by physicians in making treatment decisions.

The second label paradigm used a Total-C requirement of 200 to 240 mg/dL. The Sponsor states that a total cholesterol range of 200 to 240 mg/dL is appropriate for use given its familiarity of this measure among consumers, its consistency with national consumer initiatives, and its reasonable degree of correlation with the LDL cholesterol range of 130 to 170 mg/dL in the 1999-2002 National Health and Nutrition Examination Survey (NHANES).

The data collected and used in this study to assess the effectiveness of the labels included the actual decisions of the participants (self-assessment and purchase) and their open-ended statements as well as information that allowed assessments of individual self-selection decisions (eligibility assessment). Since no drug was dispensed in the study, there are no drug-related adverse events.

6.1.2 General Discussion of Endpoints

The objectives of the SELECT study were as follows:

- Using an LDL cholesterol label paradigm as an eligibility criterion for use, evaluate participants' ability to make self-assessment decisions that are consistent with the label and appropriate purchase decisions. Participants' self-assessment and purchase decisions were compared to their Eligibility Assessment to determine if their Self-Assessment decisions are "consistent per label" and their Purchase Decisions are appropriate.
- Using a Total cholesterol label paradigm as an eligibility criterion for use, evaluate participants' ability to make self-assessment decisions that are consistent with the label and appropriate purchase decisions. Participants' self-assessment and purchase decisions were compared to their Eligibility Assessment to determine if their Self-Assessment decisions are "consistent per label" and their Purchase Decisions are appropriate.
- To provide insight regarding participants' reasoning and factors considered when making self-assessment and purchase decisions.

MO Comment: *The Agency has informed the Sponsor that the treatment paradigm should be consistent with NCEP ATP III Guidelines which use LDL-cholesterol as the basis for determining the need for cholesterol lowering treatment and follow-up.*

6.1.3 Study Design

Recruitment. Mass media advertising for study recruitment was centrally developed and the advertising copy was very similar to that used in CUSTOM. Advertising was aimed at diverse socioeconomic and ethnic audiences at various sites throughout the US, to attract subjects concerned about their cholesterol by providing a toll-free telephone number. To ensure unbiased self-selection, the advertisements did not include any of the specific label inclusion/exclusion criteria. However, as planned in the marketplace, the advertisements stated that potential participants should know their cholesterol numbers. Radio ads stated "To participate in the study, it's important to know your four cholesterol numbers: total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. If you don't know them, call the study hotline for help 1-888-LOWER 61 for help."

Subjects who called the toll-free number were asked to provide personal and demographic information (e.g., date of birth, gender, race, name, address) to a live operator and were asked several exclusion questions not related to label criteria as listed below. The live operator did not provide a reminder to bring cholesterol values. However, as was done in CUSTOM, if a participant inquired about how to get their cholesterol numbers, they were told that they could call their doctor to get them, ask their doctor for a test, get a test elsewhere, use a home test kit, or get a cholesterol test available at the study site. All participants were told that a fast of 9 to 12 hours was required since they may need a blood test for diagnostic safety reasons. As was done in CUSTOM, participants were told that they might have the opportunity to purchase a product ($19.99 for a 45-day supply) that has been available only by prescription, but might eventually become available OTC. The purpose of this was to reduce the number of participants who would decide not to purchase because of an issue with money.

MO Comment: *Advertising may have recruited a more informed population and enriched the trial with subjects who knew their cholesterol profiles. It is not clear how to generalize the study results to the general population who may become interested in using the OTC product, unless future advertising also has similar messages.*

The exclusion criteria not related to label directions were:

- Caller could not read and understand English without assistance.
- Caller was <18 years of age.
- Caller or household member was a physician or pharmacist, or was employed by a pharmaceutical company.
- Caller has a spouse and/or a household member that had already participated in this study (spouses and/or household members could both participate in the study if their appointments were at the same time).
- Caller was referred to the study by a friend or relative who had already participated in the study.

- Caller had previously participated in a clinical study in which a cholesterol medicine was available only by purchase.

MO Comment: *SELECT should also have excluded anyone who had participated in any consumer or clinical study that involved a statin, including label comprehension studies. If a subject had previously enrolled in any such trial, they may have learned from their previous study participation, which may lead to bias in the result of this study.*

Some study site locations of SELECT overlapped with those of previous studies. The Sponsor was asked to provide information on whether any SELECT subjects also participated in previous Mevacor consumer studies. The Sponsor reported that 31 subjects in SELECT may have previously participated in CUSTOM, the actual use study for the same product. This is a potentially serious deficiency that involved, however, a small number of duplicates. Other potential overlaps between SELECT and previous Mevacor Daily studies are summarized in the Appendix.

A nurse investigator administered scripted questions to study subjects using electronic eCRFs. At the study site, subjects were told, "[thank you for] agreeing to participate in this clinical study to evaluate a potential over-the-counter medicine, MEVACOR™ Daily, which may some day be available in drugstores without a prescription. In this study, you will be given a chance to examine the product, decide whether or not it's appropriate for you to take, and decide whether or not you would like to buy it today. The price for a 45 day supply is $19.99. Throughout the study you will notice that I will be reading from a script and following a standard procedure to insure that everyone in the study receives the same information."

The participant was then told, "[here is a] package of MEVACOR™ Daily and ask you to look at it as though you were seeing it in a drugstore where you normally shop for over-the-counter medicines. MEVACOR™ Daily is not appropriate for everyone, so do what you normally would do to consider whether this product is right for you. Feel free to take as much time as you want to read the package, just as you would with any new medicine you are considering taking for the first time. And, just like in a store, please do not take the product out of the box.

I will leave you for a few minutes so you can concentrate. When I return, I will ask you: based on what you have read on this label, is this product appropriate for you to use right now, or not. I will also ask you if you would like to buy it or not. You will be able to ask me some of the questions you might ask a pharmacist before you make your decisions. I will then ask some questions to learn how you made your decisions. This is not a test of your memory, so you will have the package to refer to as we are talking about it. You should know, that even if you decide that this product is not appropriate for you to use or if you decide not to buy it, you will still receive the same compensation."

MO Comment: *Participants were told that the product is not appropriate for everyone and were told that they would be asked whether the product was appropriate for them. They were also told to concentrate and to take as much time as needed. These directions may have cued subjects to pay more attention than usual to self-selection criteria and may have led to a higher percent of correct self-selection decisions than would ordinarily occur in the consumer OTC environment.*

The participants, however, were also told to do as they normally would to consider whether the product was right for them.

Eligibility for Use of Product. For the LDL-C treatment paradigm, the label requirements for use were as follows.

- LDL cholesterol range is between 130 to 170 mg/dL and treatment goal is <130 mg/dL
- Both males and females must have an additional risk factor in addition to meeting the age criteria, which are: men 45 and older, women 55 and older. The additional risk factors, at least one of which must be present, were:
  - Hypertension or taking anti-hypertensive medications
  - Family history of heart disease in father or brother before age 55, or in mother or sister before age 65
  - Smoker
  - HDL 1 to 39

For the Total-C paradigm, the label requirements for use were as follows.

- Total cholesterol range is between 200 to 240 mg/dL
- Men meeting the age criteria (45 and older) do not need a risk factor. According to the Sponsor, the major predictors of Framingham risk assessment for men are age and total cholesterol value. Any man >45 years of age with a total cholesterol of 200 mg/dL or higher has an estimated 10-year risk for CHD of approximately 5% without the presence of any additional risk factors. The addition of a risk factor such as smoking for men will increase risk. However, eliminating the risk factor simplified the eligibility criteria for men and maintained a similar distribution of cardiovascular risk for men and women.
- Females must have an HDL of 1 to 59 and require an additional risk factor beyond meeting the age criteria. The additional risk factors are the same as listed above for the LDL-C paradigm.

MO Comment: *The Framingham 10-yr risk for CHD is 4% for a 45 year old male with Total-C of 200-239 mg/dL, and no other risk factors. Drug therapy is not recommended under ATP III guidelines at such a low risk level unless LDL is over 190 (optionally, over 160).*

Participants were ineligible to use the product based on the label, if for either treatment paradigm:

- Participant was currently taking any prescription cholesterol-lowering medication.
- Participant was a woman with HDL ≥ 60 mg/dL.
- Participant had liver disease.
- Participant had a history of heart disease, stroke, or diabetes
- Participant was taking a medication that is included in one of the following categories of prescription medications known to potentially interact with lovastatin: cholesterol medicines, oral antibiotics, oral antifungals, drugs for irregular heartbeat, HIV protease

inhibitors, cyclosporine (immune suppressants), nefazodone (antidepressant) or the participant drinks large quantities of grapefruit juice (greater than 1 quart daily).

- Participant was pregnant, breast-feeding, or thought she may become pregnant.
- Participant was allergic to lovastatin.

The corresponding warnings are in the Drug Facts section, where the first four bullets are in "Ask your doctor before use", the 5th bullet on drug interactions is in "Ask a doctor or pharmacist before use if you are", and the last two are "Do Not Use" warnings (separate sections of label).

See Section 10.2 for copies of the proposed labels.

Self-assessment. Participants reviewed the product label and were asked the following self-assessment (SA) question:
"Based on this label, is this product appropriate for you to use right now or not?" The participant's self-assessment decision was evaluated by comparing it to their Eligibility Assessment. An Eligibility Assessment uses the participants' self-reported medical history as it related to the label, where responses were considered either '**correct per label**' or '**not correct per label**'. In addition, an '**other**' category was used to represent a self-assessment decision that is not a categorical yes or no (such as, "I do not like to take any OTC medications," "I need to talk to my doctor," "I am not sure," "I don't know").

During the self-assessment questioning, participants could request a cholesterol test, ask for clarification regarding potentially interacting medications, ask to talk to a pharmacist, or ask to talk to a doctor. The investigators were trained to answer questions that a pharmacist would be able to answer, and were able to respond to questions regarding concomitant medications. If one of these requests was made, immediately after obtaining the results of their cholesterol test, receiving an answer to a question regarding concomitant medications, or receiving an answer from the investigator to a frequently asked question, the self assessment question was asked again. If the participant asked to talk to a doctor, the self-assessment question was not asked again.

However, if at any time the participant responded to the self-assessment question by saying, "yes, but I need to talk to my doctor," or "yes, but I need more information" or a response that seemed to contradict itself, the participant was re-asked the self-assessment question.

Participants with a positive self-assessment decision, who were determined to be not correct per label, were asked follow-up questions after they made their purchase decision which is described below. The responses to the follow-up questions were collected into patient profiles and evaluated to understand the thought processes that went into the decisions. In some cases, the Sponsor evaluated responses as incorrect per label but nonetheless "mitigated" if the participant made a statement indicating that the participant intended to discuss MEVACOR™ Daily with their doctor, had a justified or reasonable explanation/rationale, or had a statement indicating evidence of not understanding the SA question.

Purchase Decision. Immediately after the participant made a self-assessment decision, they were asked to make a purchase decision (PD) in response to the following question: *"Would you*

like to pay for this right now for your own use or put it back in the display?" The Sponsor considered all decisions Not to Purchase the product as correct, even if the subject was eligible per label.

MO Comment: *By classifying all decisions Not to Purchase as correct, the Sponsor increased the percentage of correct purchase decisions. This procedure affected 17/565 subjects in the LDL-C arm and 26/557 subjects in the Total-C arm (Appendix, Sponsor Tables 11-8 and 11-9).*

During the purchase decision questioning, participants could request a cholesterol test, ask for clarification regarding potentially interacting medications, ask to talk to a pharmacist, or ask to talk to a doctor. If this type of question was asked, immediately after obtaining the results of their cholesterol test, receiving an answer to a question regarding concomitant medications, or receiving an answer to a frequently asked question from the "pharmacist", the purchase decision question was asked again. If the participant asked to talk to a doctor, the purchase decision was not asked again.

If the participant decided to buy the product, they were asked the following open-ended question "After you buy this product, is there anything that you plan to do before you start using it?" This provided a better understanding of the participant's intended behavior before taking the first dose of medication, including identifying the participants who still intended to talk to their doctor.

Some participants responded to the self-assessment or purchase decision questions stating that they wanted to talk to their physician. However, unlike CUSTOM, participants were not permitted to leave the site and return for a second visit to make their self-assessment and purchase decisions.

Cholesterol and Blood Pressure Testing. If before making their self-assessment or purchase decision, a participant indicated that they needed a cholesterol test, one was offered to them at no cost. The participants who requested a cholesterol test were asked to sign an abbreviated consent form.

All participants had their sitting blood pressure measured before they received a cholesterol test. One reading for systolic and diastolic blood pressure was recorded. Blood pressure was used to calculate the Framingham 10-year CHD risk score for each participant.

Participants who did not indicate that they needed a cholesterol test prior to answering the self-assessment or purchase decision questions were not offered a test at that time. Participants who did not request a cholesterol test prior to answering these questions were administered a test at the end of the visit. This allowed the Framingham Risk score to be calculated for the entire study population, based on measured lipid values that were standardized across the study, except for participants who refused a test or had incalculable values.

Participants who indicated that they had not fasted prior to their visit, and who had requested a cholesterol test before making self-assessment and purchase decisions, may have used the results of this test to make their self-assessment and purchase decisions. However, if they made positive self-assessment or positive purchase decisions, they were considered *not correct per label* for

self-assessment and/or *not correct* for purchase decision, because the label states the product user must have had a fasted cholesterol test. Participants who indicated that they would purchase and who had not fasted were asked to return to the site fasted for another test. This test was not used to assist them in their self-assessment or purchase decisions, but was used only to calculate the Framingham risk score.

If a participant brought cholesterol values to the study site from a previous test, and these values differed from the values obtained at the site, the cholesterol numbers the participant used to make the self-selection decisions were the numbers used to assess correctness. If cholesterol values were obtained at the site at the end of the questioning, these numbers were only used to calculate the Framingham risk score and for participant education.

After the SA and PD decisions were recorded, medical history as it relates to the label was collected from subjects so eligibility determinations were made to see if the subject was eligible to use Mevacor Daily as per the label.

Mitigation and Reclassification of Data. The Sponsor reviewed each ineligibility based on the information found in the Case Report Form, to evaluate if the participants had a mitigating circumstance defined as justified or reasonable explanation/rationale for an incorrect decision. This task was performed on participants who had an SA = Yes or a PD = Yes, and who were not eligible per the label. For these participants, there were three types of potentially mitigating verbatim statements in the eCRF: 1) a statement indicating that the participant intended to discuss MEVACOR™ Daily with their doctor, 2) a statement which provided justified or reasonable explanation/rationale, 3) a statement indicating evidence of not understanding the SA question.

If a participant stated that they wanted to talk to the doctor before they made their SA or PD, the investigator completed the Talk to the Doctor eCRF. At other times during the interview, the participant may have stated in a verbatim response to an open-ended question that they wanted to check with a doctor before use or before purchasing. Participants were never asked if they wanted or needed to talk with their doctor. A talk to the doctor categorization was only considered if the participant did not have an absolute safety ineligibility. Absolute safety ineligibilities are indicated as “Do Not Use” on the MEVACOR™ Daily label. Some participants felt that if they talked to their doctor first, they were following the label when they said the product was appropriate for them or that they would buy it despite having one of these ineligibilities.

The eCRFs were reviewed for participants with verbatim responses indicating they had other potentially mitigating factors. For example, mitigating factors may have included statements such as “My age is close,” if the participant was younger than the age indicated on the label, or “I was told by my doctor I should be treated,” if the participant stated that they did not know their LDL-C value or Total-C value during the Eligibility Assessment (EA). In contrast, a participant who stated that they “Believed or thought their LDL-C or Total-C was high” or that they had “family history” was not given a mitigating factor.

A specific mitigating factor that applies only for SA decisions is "Evidence of Not Understanding SA Question." This indicates that a participant's response to an open-ended question provided clear evidence that they were either not thinking of the question in terms of "right now" or that they were thinking in theoretical terms. A common example of this is a participant that responded "Yes" to the SA question and "No" to the PD question. When asked why they did not wish to buy the product, a participant labeled as "evidence of not understanding SA question" may have stated that they did not want to buy because they did not meet an eligibility criterion. Obviously, this participant understood the label, knew they were ineligible, and did not want to use the product. Another example is a participant who was already taking lipid lowering medication. This participant may have responded SA=Yes and PD=No and responded that they do not need a statin since they are already taking one.

MO Comment: *The Sponsor mitigated subjects who said their doctor told them to be treated, but OTC statin treatment may not be appropriate in all such cases (for instance, if they are at high risk or have CHD).*

The Sponsor also reclassified several cases (11 cases in the LDL-C arm, 6 in the Total-C arm) from incorrect to correct, based upon review of the open-ended response data. For example, a participant may have responded that they actually did not have diabetes, they simply had high blood sugar, or that they did not have a heart problem, they had a heart murmur when they were an infant. Other participants who responded SA=No and PD=Yes were challenged on reasons why they were not eligible. There were instances of participants indicating an ineligibility that did not apply for their allocated paradigm. In these cases, these participants were marked as correct for the applicable ineligibility criterion.

MO Comment: *The reclassification of these cases does not appreciably affect results.*

Statistics. The study did not have any formal Study Hypotheses. For each of the two label paradigms, 95% confidence intervals were calculated for the following for each label paradigm:

- Proportion of participants who made consistent per label yes or no self-assessment decisions.
- Proportion of participants who made appropriate yes or no purchase decisions.

Demographic and Other Subgroups. The study was neither designed nor powered for subgroup analyses. However, there were several subgroups of interest for efficacy analyses. These subgroups were defined based on gender, age, race, and literacy level. Literacy level was assessed using the Rapid Estimate of Adult Literacy in Medicine (REALM) Test. The Sponsor reported no significant differences by any of these subgroups, including the low literate group.

The typical participant who responded SA=Yes had a primary care physician, health insurance, tried diet and exercise, was well educated, and was middle class based on annual income. Table 6 displays the distribution of participants' highest educational level and household income before taxes by SA and PD. More than 90% of participants indicated they graduated high school, and approximately 60% reported at least some college education. Household incomes were distributed from less than $20,000 to $90,000, with 43% of participants reporting an annual household income of $40,000 or less, and 36-40% reporting an income of more than $40,000 up

to $90,000. No important differences were observed between participant SA and PD Yes and No decisions among the education and income subgroups.

Table 6. Education and Income Distributions, Two Study Arms Combined

	Self Assessment			Purchase Decision	
	Yes (N=495) n (%)	No (N=915) n (%)	Other (N=88) n (%)	Yes (N=431) n (%)	No/Other (N=1063) n (%)
Educational Level:					
Elementary school only	4 (0.8)	7 (0.8)	2 (2.3)	4 (0.9)	9 (0.8)
High school incomplete	34 (6.9)	65 (7.1)	5 (5.7)	24 (5.6)	78 (7.3)
High school graduate	128 (25.9)	214 (23.4)	27 (30.7)	117 (27.1)	253 (23.8)
Vocational/Technical	26 (5.3)	63 (6.9)	6 (6.8)	25 (5.8)	70 (6.6)
College incomplete	115 (23.2)	206 (22.5)	21 (23.9)	93 (21.6)	249 (23.4)
Associate's degree	48 (9.7)	87 (9.5)	7 (8.0)	47 (10.9)	93 (8.7)
Bachelor's degree	84 (17.0)	172 (18.8)	12 (13.6)	72 (16.7)	197 (18.5)
Postgraduate/advanced college degree	55 (11.1)	101 (11.0)	8 (9.1)	49 (11.4)	113 (10.6)
Refused	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Household Income Before Taxes:					
<20,000	83 (16.8)	155 (16.9)	17 (19.3)	65 (15.1)	190 (17.9)
20,000 - 40,000	116 (23.4)	251 (27.4)	25 (28.4)	100 (23.2)	288 (27.1)
40,001 - 60,000	110 (22.2)	171 (18.7)	25 (28.4)	95 (22.0)	210 (19.8)
60,001 - 90,000	81 (16.4)	147 (16.1)	10 (11.4)	77 (17.9)	161 (15.1)
>90,000	70 (14.1)	138 (15.1)	9 (10.2)	73 (16.9)	145 (13.6)
Refused	24 (4.8)	37 (4.0)	2 (2.3)	15 (3.5)	48 (4.5)
Don't Know	11 (2.2)	16 (1.7)	0 (0.0)	6 (1.4)	21 (2.0)

Study Population and Participant Disposition. According to the Sponsor, there were 5107 people who called the call center in response to an advertisement for cholesterol-concerned individuals. The randomized study population was 1520 (767 to the LDL-C arm, 753 to the Total-C arm). Of these, 21 subjects did not complete the study (13 from the LDL-C arm, 8 from the Total-C arm). The age range among subjects was 18 to 86. Those who completed the study numbered 1499, where 754 were in the LDL-C arm and 745 were in the Total-C arm. Two additional participants were excluded from efficacy analyses as protocol violators: one because a household member had already participated in the study, and another at a different site who was referred by a friend or relative. Hence the efficacy population, both arms combined, was 1497.

See Figure 1 for an accounting of the study participants.

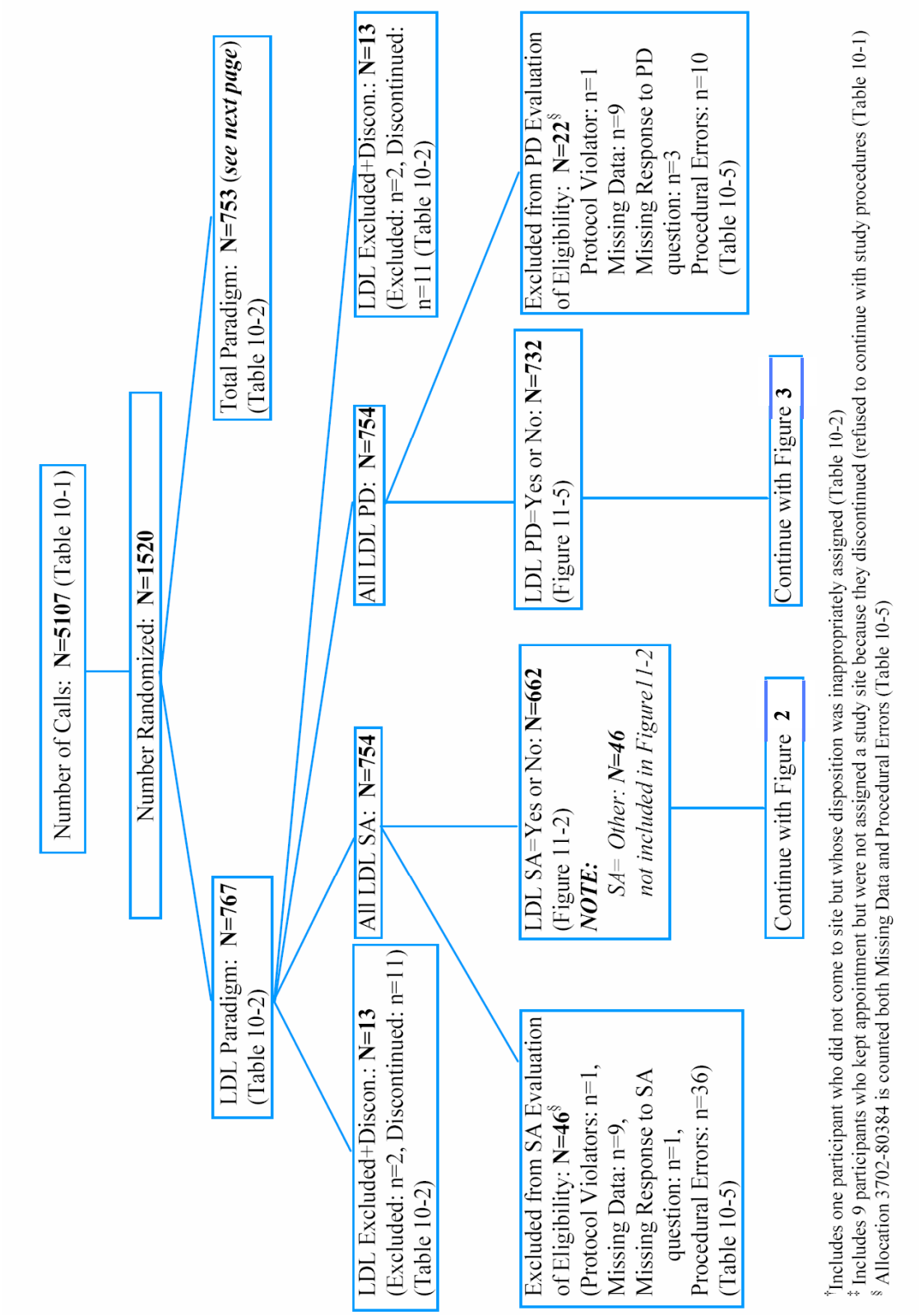


Figure 1. SELECT Study Patient Disposition

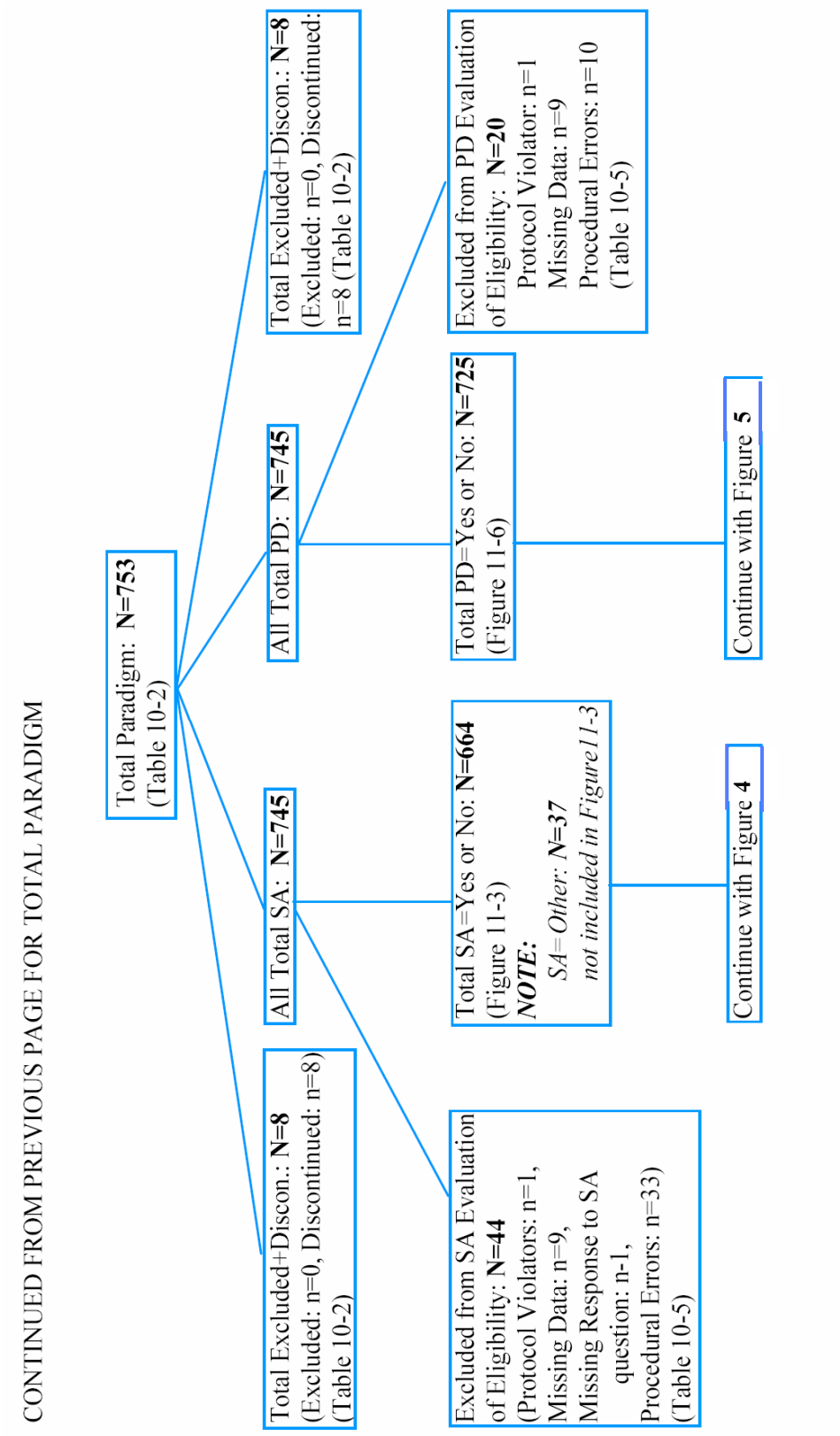


Fig. 1 continued.

MO Comment: *The study enrolled fewer than 30% of the consumers who contacted the call center. Common reasons for not enrolling were: study sites were too far away or inconvenient, the subject did not want to pay, or the caller was already on a statin. The number of participants by study site was given in Sponsor Table 10-1 (see Appendix). Sponsor Table 10-1 contains apparent errors in the second column, where the numerical entries and percentages are not consistent with the column total of 5107.*

Additional demographic information is given in Sponsor Tables 10-8 and 10-9 (see Appendix). The study population, both arms combined, consisted of about 52% females (age range 18-86), and 48% males (age range 18-86). A 19 year-old female selected SA=Yes in the Total-C arm, and a 24 year-old female selected SA=Yes in the LDL-C arm. Both were mitigated (see Mitigation of Ineligibility section) because they said they would talk to a doctor.

The Sponsor discussed several procedural issues that affected a small portion of the data. Two participants were missing SA data (one in each arm) and 3 participants were missing their PD data (all in the LDL-C arm). Eighteen participants were missing data that prevented the assessment of eligibility, nine in each arm. The participants with missing eligibility assessment data are not included in any summaries evaluating their SA and PD versus their eligibility assessment.

In addition to the missing data, there were two types of procedural errors relating to the cholesterol test. The first error occurred when the investigator provided the participant with a cholesterol test after they made their final PD but before they responded to the Eligibility Assessment questions pertaining to cholesterol. According to the protocol, cholesterol tests were not to be provided after the final purchase decision was made. Because of this error, it is not possible to know what cholesterol numbers the participant used when making their self-selection decisions (SA and PD). This occurred with 20 participants. These participants are not included in any summaries evaluating their SA and PDs versus their eligibility assessment, since a true eligibility assessment based on the information the participant had at the time of making these decisions is unknown. These participants were found by reviewing the SA and PD data. If a request for a cholesterol test was not found, the audit trail for the participant was reviewed.

The second type of procedural error was a minor design flaw in the phrasing of the eligibility assessment question. Specifically, in the study, it was possible for a participant to request a cholesterol test after they made their SA decision but before they made their final PD. Because of the phrasing of the eligibility question, it is not possible to know what cholesterol numbers the participant used when making their SA decision. This procedural error occurred with 49 participants. These participants are not included in any summaries evaluating their SA decisions versus their eligibility assessment since the eligibility assessment is not valid for the SA decision. These participants are included in summaries for PD and in other summaries unless otherwise noted.

Overall**,** 69 participants are excluded for SA when the 20 participants who had the first type of procedural error are added to the 49 participants with the second type of procedural error. The total SA population, for combined Yes, No, and Other responses, was 1409. The total PD population was 1457. See Table 7 for the Sponsor's summary of patient disposition.

Table 7. SELECT Patient Disposition, Two Study Arms Together And Individually

Combined Paradigm	Count (n)			
Self-Assessment:	**All SA**	**SA=Yes**	**SA=No**	**SA=Other**
Completed Study	**1499**	**494**	**916**	**87**
Excluded from Evaluation of overall Eligibility Assessment for SA	**90**	**38**	**46**	**4**
Protocol Violators	2	0	2	0
Missing Data (included in individual criteria summaries if available)	18†	7†	11	0
Missing Response to SA Question	2			
Procedural Errors related to timing of a requested cholesterol test	69†	32†	33	4
Purchase Decision:	**All PD**	**PD=Yes**	**PD=No**	-
Completed Study	**1499**	**431**	**1065**	
Excluded from Evaluation of overall Eligibility Assessment for PD	**42**	**12**	**27**	
Protocol Violators	2	0	2	
Missing Data (included in individual criteria summaries if available)	18†	6†	12	
Missing Response to PD Question	3			
Procedural Errors related to timing of a requested cholesterol test	20†	7†	13	

† Allocation Number '3702-80384' is counted in both 'Missing Data' and 'Procedural Errors related to timing of a requested cholesterol test'.
PD = purchase decision; SA = self assessment.

LDL-C Paradigm	Count (n)			
Self-Assessment:	**All SA**	**SA=Yes**	**SA=No**	**SA=Other**
Completed Study	**754**	**235**	**471**	**47**
Excluded from Evaluation of overall Eligibility Assessment for SA	**46**	**21**	**23**	**1**
Protocol Violators	1	0	1	0
Missing Data (included in individual criteria summaries if available)	9†	4†	5	0
Missing Response to SA Question	1			
Procedural Errors related to timing of a requested cholesterol test	36†	18†	17	1
Purchase Decision:	**All PD**	**PD=Yes**	**PD=No**	-
Completed Study	**754**	**203**	**548**	
Excluded from Evaluation of overall Eligibility Assessment for PD	**22**	**7**	**12**	
Protocol Violators	1	0	1	
Missing Data (included in individual criteria summaries if available)	9†	4†	5	
Missing Response to PD Question	3			
Procedural Errors related to timing of a requested cholesterol test	10†	4†	6	

† Allocation Number '3702-80384' is counted in both 'Missing Data' and 'Procedural Errors related to timing of a requested cholesterol test'.
PD = purchase decision; SA = self assessment.

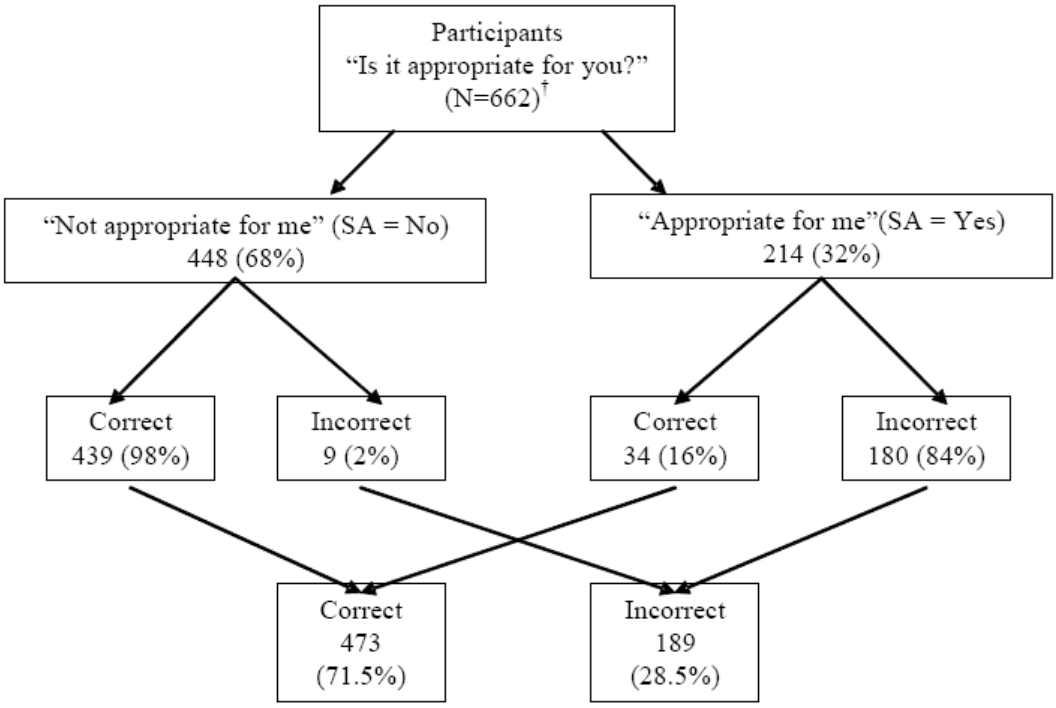
Total-C Paradigm	Count (n)			
Self-Assessment:	***All SA***	***SA=Yes***	***SA=No***	***SA=Other***
Completed Study	***745***	***259***	***445***	***40***
Excluded from Evaluation of overall Eligibility Assessment for SA	**44**	**17**	**23**	**3**
Protocol Violators	1	0	1	0
Missing Data (included in individual criteria summaries if available)	9	3	6	0
Missing Response to SA Question	1			
Procedural Errors related to timing of a requested cholesterol test	33	14	16	3
Purchase Decision:	***All PD***	***PD=Yes***	***PD=No***	**-**
Completed Study	***745***	***228***	***517***	
Excluded from Evaluation of overall Eligibility Assessment for PD	**20**	**5**	**15**	
Protocol Violators	1	0	1	
Missing Data (included in individual criteria summaries if available)	9	2	7	
Missing Response to PD Question	0			
Procedural Errors related to timing of a requested cholesterol test	10	3	7	

MO Comment: *Across both arms, a majority of participants elected not to use (over 60%) and/or not to purchase (close to 70%). The numbers of subjects excluded from efficacy analyses because of procedural difficulties were (from the LDL-C arm) 46 for SA and 22 for PD; excluded from the Total-C arm were 44 subjects for SA and 20 subjects for PD.*

There are minor inconsistencies in the study report concerning accounting of patient disposition and other results. The total SA population was also calculated as 1408 = 1499 - (2+18+20+49+2), but according to Table 7 it is 1409 = 1499 – 90.

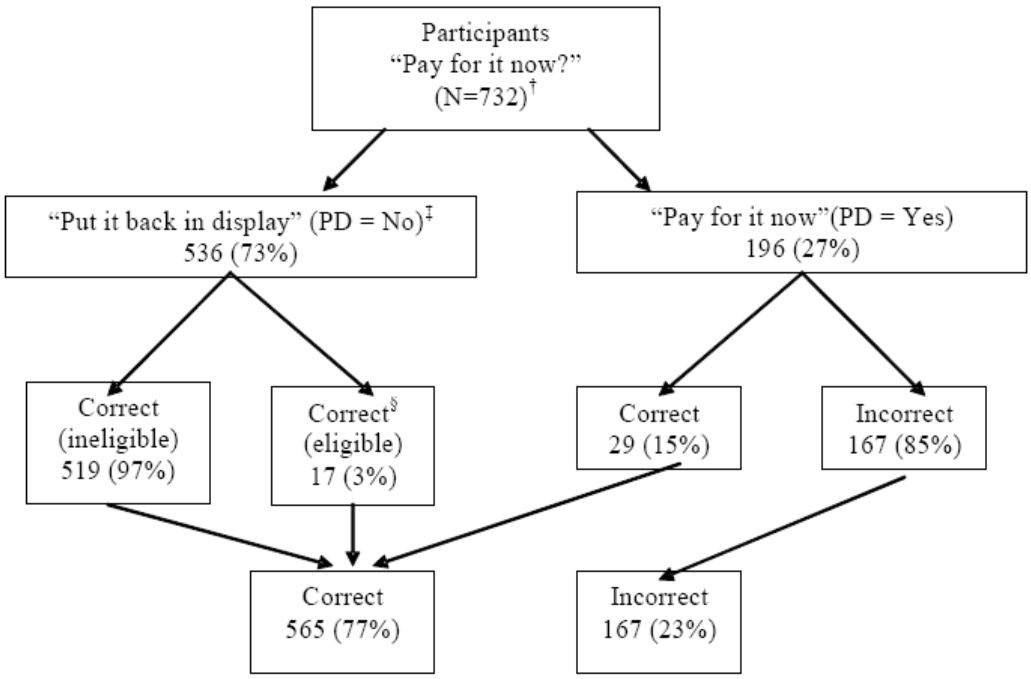
6.1.4 Efficacy Findings

The efficacy population statistics for the LDL-C arm are summarized in Figure 2 and in Figure 3. The efficacy population for SA was 662, while that for PD population was 732. Of these final populations, 32% had SA=Yes and 68% had SA = No, while 27% had PD=Yes and 73% had PD=No.



† Does not include the 46 participants who did not provide an SA decision, 1 participant with a missing SA, and 45 participants who were protocol violators, had missing EA data, or had a cholesterol test after SA but before completing their EA.
EA = eligibility assessment; SA = self-assessment.

Figure 2. Flowchart of SA Decisions for LDL-C Arm

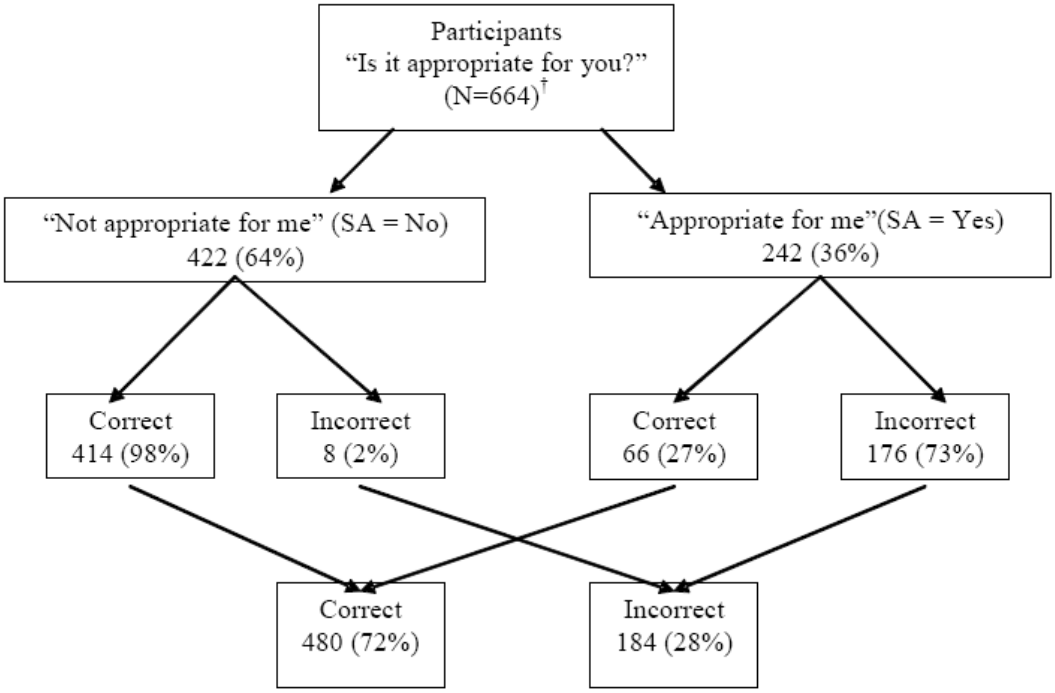


† Does not include 3 participants with missing purchase decision and 19 participants who either were protocol violators, had missing EA, or had cholesterol test after purchase decision before EA.
‡ Participants who did not definitely provide a yes or no response were classified as a "no" since purchasing is a binary decision (either you say you want to pay for it right now, or not).
§ Although these participants chose not to purchase the product despite being eligible, their responses are considered correct since it is never wrong to not purchase the product.
EA = eligibility assessment; PD = purchase decision.

Figure 3. Flowchart of PD Decisions for LDL-C Arm

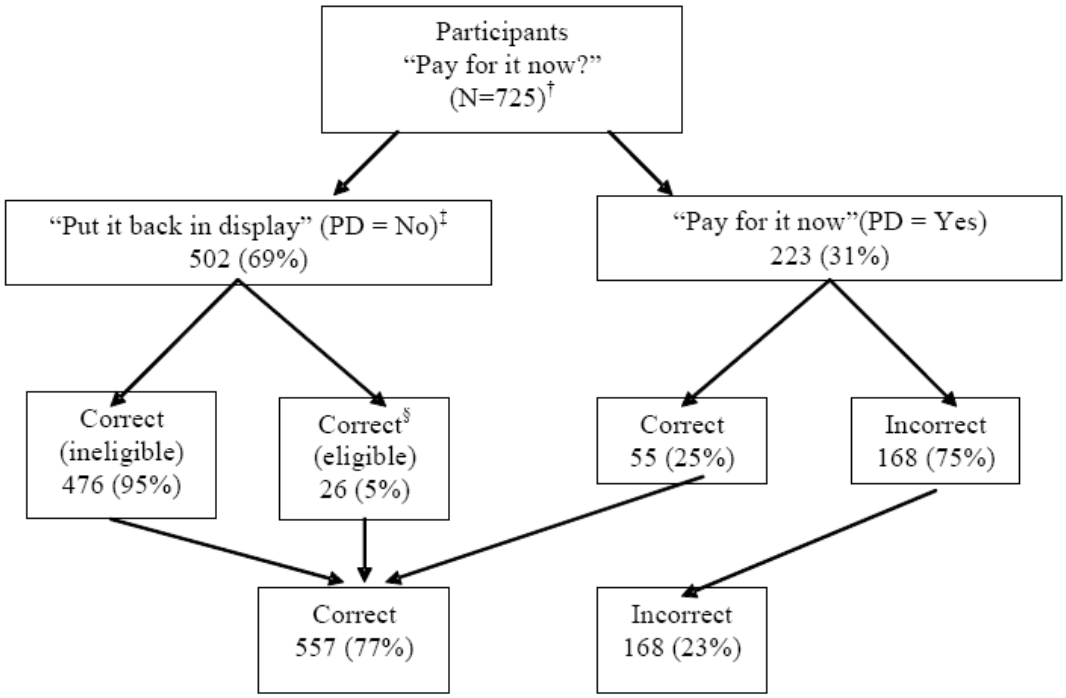
MO Comment: *In the LDL-C arm, a high percentage (98%) of subjects who decided SA = No did so correctly, but a low percentage (16%; 95% CI per FDA statistician, 11.3% to 21.5%) of subjects who chose SA=Yes did so correctly. A similar result is found for PD, with a very high percentage of correct decisions not to purchase and a much lower percentage of correct decisions to purchase. The overall percentages of subjects with correct decisions (72% for SA, 77% for PD) are dominated by subjects who decided that the product was not appropriate to use (SA = No) or decided not to purchase (PD=No). This reviewer believes that the percentages of correct decisions are more important for those subjects who thought the product was appropriate for use or who decided to purchase the product.*

The efficacy population statistics for the Total-C arm are summarized in Figure 4 and in Figure 5. The efficacy population for SA was 664, while that for PD population was 725. Of these final populations, 36% had SA=Yes and 64% had SA = No, while 31% had PD=Yes and 69% had PD=No. Figure 4 displays the self-assessment decisions made by 664 participants in the Total-C paradigm. The percentage of correct SA decisions was 72.3% with a 95% CI (68.7%, 75.7%).



† Does not include 41 participants who did not provide an SA decision, 1 participant with a missing SA, and 43 participants that were protocol violators, had missing EA data, or had a cholesterol test after making their SA but before completing their EA.
EA = eligibility assessment; SA = self-assessment.

Figure 4. Flowchart of SA decisions for Total-C Arm



† Does not include 20 participants who were protocol violators, had missing EA, or had cholesterol test after purchase decision before EA.
‡ Participants who did not definitely provide a yes or no response were classified as a "no" since purchasing is a binary decision (either you say you want to pay for it right now, or not).
§ Although these participants chose not to purchase the product despite being eligible, their responses are considered correct since it is never wrong to not purchase the product.
EA = eligibility assessment; PD = purchase decision.

Figure 5. Flowchart of PD for Total-C Arm

MO Comment: *In the Total-C arm, as in the LDL-C arm, a high percentage (98%) of subjects who decided SA = No did so correctly, but a low percentage (27%; 95% CI per FDA statistician, 21.8% to 33.4%) of subjects who chose SA=Yes did so correctly. The 72% percentage of correct SA decisions was dominated by subjects who selected* ***SA=No****. A similar result is found for PD, with a very high percentage of correct decisions not to purchase and a much lower percentage of correct decisions to purchase. This reviewer believes that the percentages of correct decisions are more important for those subjects who thought the product was appropriate for use or who decided to purchase the product.*

Mitigation of Ineligibility. The numbers of subjects evaluated by the sponsor as ineligible but who gave open-ended responses that potentially mitigate their incorrect SA=Yes responses are summarized in Table 8. The most common responses that were considered to mitigate an incorrect SA decision were those in which the participant indicated a desire to talk to a doctor at some point. There were several mitigating factors identified for each ineligibility criterion.

Table 8. Numbers of Subjects with Open-Ended Responses that Potentially Mitigate Incorrect Self-Assessment (SA=Yes)

Paradigm	Incorrect vs. EA (n†)	Talk to Doctor (n†‡)	1 Mitigated Ineligibility (n†)	≥2 Mitigated Ineligibilities (n†)	Evidence of Not Understanding SA Question (n†‡)	Total Mitigated (n†)
LDL	180	46	12	11	16	85
Total Cholesterol	176	30	26	6	11	73

† Participants with missing data, participants whose eligibility could not be determined due to a data collection issue, and protocol violators are excluded.
‡ If a participant stated that they wanted to 'Talk to a Doctor' and other open-ended responses demonstrated 'Evidence of not understanding SA', the participant was only counted under the 'Talk to Doctor'.
EA = eligibility assessment; SA = self assessment.

MO Comment: *Almost half of ineligible subjects (85/180) were mitigated in the LDL-C arm and 73/176 (41%) were mitigated in the Total-C arm by the Sponsor, most often because an intent was expressed to talk to a doctor. This reviewer agrees that many, but not all, of the mitigating factors identified by the Sponsor in the open-ended responses may provide a reasonable basis for allowing treatment. Table 9 shows the results of analysis by the DNCE review team, which examined the 55 cases in the columns "1 Mitigated Ineligibility" and "≥2 Mitigated Ineligibilities," as well as the 27 cases under "Not Understanding SA…"and the 76 cases under "Talk to Doctor".*

In the LDL-C arm, 46/85 ineligible subjects were mitigated by the Sponsor because the subject said he/she would talk to a doctor (similarly, 30/73 cases mitigated for this reason in the Total-C arm). Although subjects were not explicitly asked whether they wanted to talk to a doctor, they were given several opportunities to do so. The first applied to those who expressed uncertainty regarding SA; in this case follow-up questions on why could have elicited the "talk to doctor" responses on which mitigation was based. The second opportunity came immediately after the PD question, unless subjects said immediately that they would not buy. If they said PD=Yes, they were asked if there was anything they plan to do first before using the product and what that would be. Participants may have stated that they wanted to talk to their doctor, providing the basis for mitigation. The third opportunity came for subjects who gave an incorrect SA, in which case they were informed of their incorrect response and then asked to give reasons why they thought the product was appropriate for their use; the participant could provide a "talk to doctor" statement at this point in the interview. And last, for those participants who responded that the product was not appropriate for use, but responded that they wanted to purchase the product, a last opportunity was provided to provide reasons for their responses. The DNCE review team found it difficult to assess the subjects' original intentions after reading the label but prior to the interactions with the interviewer. The subject could have been brought to the realization that they should ask a doctor by the interview questioning. Nevertheless, this reviewer gave the benefit of the doubt, in that "talk to a doctor" was accepted for mitigation if mentioned in any of the opportunities.

An additional issue is that even if the subject expresses an intention to talk to a doctor, the SELECT study has no means to evaluate whether the subject would actually do so if able to purchase the product OTC.

Also in the LDL-C arm, 23/85 subjects were mitigated because the Sponsor felt that the subjects provided an acceptable rationale for their incorrect responses (in the Total-C arm, 32/73

mitigated for this reason). In many cases, the mitigation was based on statements that the subjects had been told by a doctor at some time in the past to take cholesterol medication. However, the DNCE review team did not agree in all such cases. Specifically, we did not agree to mitigate the subject if he/she was prescribed a more potent prescription statin (e.g., case 3789-81284, Table 9*). Also, the FDA team did not agree to mitigate if the subject was a CHD risk equivalent (e.g., case 5503-81688,* Table 9*) and should be followed by a physician for cholesterol treatment, or if the subject was low risk and should not necessarily take any statin. Finally, the DNCE team did not agree to mitigate if the subject previously stopped using a prescription statin because of an AE (e.g., muscle pain: case 6983-83155,* Table 9*). This reviewer did agree to mitigate the subject if high cost, which the subject said he/she could not afford, was the only reason for stopping their previous prescription statin and wanting to use and/or purchase OTC Mevacor.*

In the LDL-C arm, the sponsor mitigated 16/85 subjects for evidence of not understanding the SA question (in the Total-C arm, 11/73 subjects mitigated for this reason). In these cases, the investigator felt that the subject was confused. The sponsor removed these cases from the label assessments (that is, these subjects were removed from the denominators of Table 10 *below). This reviewer feels that these cases should not be removed from the denominator, since these subjects did participate in the study and may have been confused by the label. However, this reviewer does feel that some of these cases can be mitigated, that is, removed from the numerator of the incorrect response proportions. If the subject gave evidence of understanding that he/she was actually ineligible, then mitigation was accepted, but if the subject gave inappropriate reasons for not purchasing after saying SA=Yes mitigation was not accepted.*

Table 9 *is not an exhaustive listing of cases where Division of Nonprescription Clinical Evaluation (DNCE) reviewers did not agree with the mitigation. The decision whether to mitigate is subjective. Three clinical reviewers in DNCE examined the verbatim responses and participant profiles of mitigated subjects, and the following cases are those where at least two reviewers out of three agreed not to mitigate.*

Table 9. Examples of Mitigated subjects where DNCE Analysis did not Agree with Mitigation

Subject #	Incorrect SA=Yes	Reason Should Not be Mitigated
2973-84568 * LDL-C arm	Female <55 LDL=199 (Total-C 281)	States she wants to lower her numbers using a low potency medication. Dr. wrote prescription for Lipitor. Has not filled it. ***Did not say she would talk to a Dr. before using.***
3789-81284 * LDL-C arm	Female 70 Diabetes Does not know LDL/HDL	States her Dr. planned to prescribe Crestor. Participant said she would not want to ask her doctor about this product because he was already going to prescribe cholesterol-lowering medication. ***Did not say she would talk to a Dr. before using.***
3856-81135 LDL-C arm	Male 64 LDL=111 (Total-C=190) Heart Disease,	States that he can not get additional supplies after 45 days; his doctor would not approve of it. Previously took an unspecified cholesterol medicine. Stopped without consulting a doctor because of side effects (muscle pain and gallstones). ***Did not say he would talk to a Dr. before using.***
3902-80335* LDL-C arm	Male 72 Heart Disease LDL=171 or higher	States previously took an unspecified cholesterol medicine. Stopped in consultation with doctor because he was hesitant about statins, did not realize Mevacor was a statin ***Did not say he would talk to a Dr. before using.***
4049-80868* LDL-C arm	Female 61 Does not know Total chol/HDL	States Dr. told her cholesterol is bad and to take cholesterol medication. Stated that she does not ask a doctor about a new OTC product before using. ***Did not say she would talk to a Dr. before using.***

Subject #	Incorrect SA=Yes	Reason Should Not be Mitigated
6014-82775* LDL-C arm	Male 57 Heart Disease LDL 165	States that he previously took this type of medication, wants to lower cholesterol, less expensive than prescription (suppose to be taking statins daily, lost insurance and couldn't afford it, anything is better than nothing, the statins the doctor had him on were four time higher. Now has insurance. ***Did not say he would talk to a Dr. before using.***
6473-84391* LDL-C arm	Female age 34 Don't know LDL Cholesterol >240	States that because of family history and her cholesterol being high her Dr. told her to take a cholesterol medication. Previously took a cholesterol medication; stopped in consultation with her doctor due to side effect of water weight gain. ***Did not say she would talk to a Dr. before using.***
6965-84449* LDL-C arm	Female 63 LDL=203 Total294 HDL=61	States Dr. said cholesterol too high and gave her a prescription for Lipitor which she has not filled yet. ***Did not say she would talk to a Dr. before using.***
6983-83155* LDL-C arm	Female 70 LDL=230 Total324 No risk factors	States previously took Zocor, stopped in consultation with doctor due to side effects (muscle aches, pains) ***Did not say she would talk to a Dr. before using.***
6541-84910* Total-C arm	Male 43 Total: 420 LDL: >171 HDL: 1-39	Too young. On Rx for lipids. Total too high. On Rx for lipids (Lipitor and Niaspan): Take in place of current medication (would stop the current cholesterol medications before starting this) -Total too high: Want to lower my cholesterol (something new and different is worth a try). ***Did not say he would talk to a Dr. before using.***
2029-84195* Total-C arm	Male 48 Heart disease Total 293 from test site	Previously took an unspecified cholesterol medicine; stopped in consultation with doctor because cholesterol numbers improved. His numbers have gone back up, so he said that his doctor was considering putting him back on cholesterol medicine. Does not ask doctor about new OTC products before using. ***Did not say he would talk to a Dr. before using.***
2476-83818* Total-C arm	Female 68 Heart disease Total: 224 LDL: 135	States had heart problems/disease and wants to lower cholesterol. Previously took an unspecified cholesterol-lowering drug; stopped without consulting doctor because of cost. Now has insurance. ***Did not say she would talk to a Dr. before using.***
3607-81735 Total-C arm	Male 61 Total: 247 HDL too low On Rx for blood pressure	Sponsor mitigated because total cholesterol is close to appropriate range. However Framingham is 25%. ***Did not say he would talk to a Dr. before using.***
3805-80740 Total-C arm	Male 52 Total: 254 LDL: 200 HDL: 35	Total too high: Cholesterol is close to appropriate range (it is not far over what is recommended); does not ask doctor about new OTC products before using. Total cholesterol level is deceptive and not reflective of LDL level in this situation. ***Mevacor 20 mg is unlikely to get the subject to LDL goal < 130.***
3859-81234* Total-C arm	Male 44 Total: 279 LDL: 210 HDL: 46	Total too high: Cholesterol is close to appropriate range (feels his numbers are close enough). Previously took an unspecified cholesterol medicine; stopped without consulting doctor and was trying fish oil. ***Mevacor 20 mg is unlikely to get the subject to LDL goal < 130.***
3948-80146* Total-C arm	Female, 74 y.o. -No risk factors Total: 214 LDL: 120	Previously took an unspecified prescription cholesterol drug 15 years ago; stopped without consulting doctor because "cholesterol went down enough"; from profile, should not be taking statins and should consult doctor before use.
4051-80359* Total-C arm	Male 48 Don't Know Total/LDL	Family History, on Rx for BP. Previously taken this type of medication (because the 20 mg dose is the same as his previous Rx for simvastatin); I know my numbers are bad/high (knows his total cholesterol was and probably is high). Framingham 25%. ***Was previously taking more potent statin. Mevacor 20 mg is unlikely to get the subject to LDL goal < 130.***
4196-80444* Total-C arm	Female 67 Total 168 LDL 96	had taken Lipitor, dosage unspecified; stopped without consulting doctor because of muscle pain and leg pain. ***Did not say she would talk to a Dr. before using.***

Subject #	Incorrect SA=Yes	Reason Should Not be Mitigated
5015-83298 Total-C arm	Male 52 Total 245 Smoker. High BP	Intends to check cholesterol numbers prior to using.. Number may not be accurate (does not know what cholesterol really is; been a year since checked; probably between 200 - 240 but may be higher; doctor told him to watch diet and he has not, so assumes it is up and he needs medicine). Is correct, Total-C is actually 299. Sees primary care doctor less than once per year. ***Patient's cholesterol should be treated by his physician.***
5503-81688* Total-C arm	Male 49 Diabetes Measured Total-C 279	Previously took an unspecified cholesterol medicine; stopped because the samples ran out and he has not been back to the doctor. High risk; c***holesterol treatment should be under physician supervision.***

*subjects stated that their MD told them to take cholesterol medication, their cholesterol should be treated, or they have taken cholesterol medications in the past

Table 10 summarizes the Sponsor's results for self-assessment in both study arms, including participants who responded yes or no to the SA question. Participants who gave an "other" response are not included in the summarization.

Table 10. Label Efficacy for Self-Assessment Including Mitigation from Open-Ended Responses

Label Paradigm	SA Response	% Completely Correct	% Correct Plus Talk to Doctor and Mitigated	% Correct Plus Talk to Doctor and Mitigated, Excluding Those Not Understanding SA
LDL-C	Yes and No	473/662 (71.5%)	542/662 (81.8%)	542/646 (83.9%)
	Yes	34/214 (15.9%)	103/214 (48.1%)	103/198 (52.0%)
	No	439/448 (98.0%)	N/A	N/A
Total-C	Yes and No	480/664 (72.3%)	542/664 (81.6%)	542/653 (83.0%)
	Yes	66/242 (27.3%)	128/242 (52.9%)	128/231 (55.4%)
	No	414/422 (98.1%)	N/A	N/A
SA = self assessment.				

MO Comment: *Of most importance in Table 10 are the rates of correct self-assessment for subjects in the two study arms who responded SA=Yes (appropriate for use). In both arms, the rates of completely correct SA=Yes decisions was low (15.9% and 27.3%, for LDL-C and Total-C, respectively). The combined rates of correct and Sponsor-mitigated SA=Yes responses are increased to about half in both arms, which are still low. The final column shows the effect of further excluding subjects who may have not understood the SA question properly; this final increase leaves the percentage of correct and mitigated SA=Yes responses, after exclusions, at low values of 52% and 55.4%, for LDL-C and Total-C, respectively.*

Although the DNCE reviewers did not agree with some of the mitigations, the numbers of cases mitigated do not appreciably alter the results in Table 10 for percent correct plus mitigated, and for that with an allowance for those not understanding SA.

MO Comment: *For both study arms, any woman past her 54th birthday was considered correct per label for the age criterion, which requires users to be age 55 or older. Also for both study*

arms, any man was considered correct per label for the age criterion if past his 44th birthday, although the label requires age 45 or older. This procedure slightly improves the stated results.

As was the case for the CUSTOM study, the results of Table 8 *and* Table 10 *suggest that significant numbers of participants rely on their physicians for their decisions to use the drug.*

Prevalence of Ineligibilities. There is a slight discrepancy in the population accounting for prevalence of ineligibility criteria in the LDL-C arm, where N=753 in Sponsor Table 10-10, but N=752 in Sponsor Tables 11-17 and 11-19. The latter is reproduced here as Table 11, which shows the prevalence of various ineligibilities among subjects in the LDL-C arm.

Table 11. Prevalence of Ineligibilities for LDL-C Arm

LDL-C Paradigm Ineligibility Criteria	Prevalence (SA)† N‡ (%) (% of evaluators with criteria)	SA=Yes† N (%) (% among those with criteria)	Prevalence (PD)† N§ (%) (% of evaluators with criteria)	PD=Yes† N (%) (% among those with criteria)
Too young	290/752 (38.6)	41/290 (14.1)	290/750 (38.7)	44/290 (15.2)
Pregnant or breast-feeding¶	2/391 (0.5)	0/2 (0.0)	2/391 (0.5)	0/2 (0.0)
May become pregnant¶	12/391 (3.1)	1/12 (8.3)	12/391 (3.1)	0/12 (0.0)
Heart problem/disease	68/752 (9.0)	33/68 (48.5)	68/750 (9.1)	22/68 (32.4)
Stroke	26/752 (3.5)	9/26 (34.6)	26/750 (3.5)	7/26 (26.9)
Diabetes	79/752 (10.5)	25/79 (31.6)	79/750 (10.5)	15/79 (19.0)
Liver disease/liver problem	23/752 (3.1)	2/23 (8.7)	23/750 (3.1)	2/23 (8.7)
Allergic to the ingredient	4/750 (0.5)	0/4 (0.0)	4/748 (0.5)	0/4 (0.0)
Medication to lower blood lipid, cholesterol or triglycerides	140/750 (18.7)	44/140 (31.4)	138/748 (18.4)	27/138 (19.6)
Taking other listed prescription medicines	12/751 (1.6)	3/12 (25.0)	12/749 (1.6)	1/12 (8.3)
Don't know HDL-C number‖¶	157/371 (42.3)	30/157 (19.1)	157/386 (40.7)	28/157 (17.8)
HDL-C is too high‖¶	88/373 (23.6)	25/88 (28.4)	93/388 (24.0)	29/93 (31.2)
Don't know LDL-C number‖	268/714 (37.5)	60/268 (22.4)	271/738 (36.7)	52/271 (19.2)
LDL-C is too low‖	153/714 (21.4)	26/153 (17.0)	162/738 (22.0)	22/162 (13.6)
LDL-C is too high‖	122/714 (17.1)	52/122 (42.6)	127/738 (17.2)	56/127 (44.1)
Drink large quantities of grapefruit juice	1/747 (0.1)	0/1 (0.0)	1/745 (0.1)	0/1 (0.0)
Used cholesterol numbers from non-fasted test	17/285 (6.0)	0/17 (0.0)	17/283 (6.0)	2/17 (11.8)
Don't have any of the listed risk factors	202/752 (26.9)	45/202 (22.3)	201/750 (26.8)	40/201 (19.9)

† Protocol violators are excluded.
‡ Excludes 1 participant with missing SA.
§ Excludes 3 Participants with missing PD.
‖ Participants who were identified as having a procedural error which related to obtaining a cholesterol test and their SA or PD decisions were not included in respective decision categories.
¶ Eligibility questions were only asked to female participants.
PD = purchase decision; SA = self assessment.

MO Comment: *In the first column of Table 11 are listed the 17 ineligibility criteria for the LDL-C label. The first of these was "age too young" (see previous MO Comment), for which the prevalence is given in the second column (SA) as: there were 290 subjects too young, out of 752 who gave an SA response and an age, giving a proportion of 38.6%. The third column gives the corresponding prevalence of specific label ineligibilities in those who said SA=Yes: 41 subjects out of 290 who were too young said SA=Yes, for a proportion 14.1%. From Sponsor Table 11-17 (see Appendix), there were 235 subjects who responded SA=Yes, so 41/235 (17.4%) of subjects who said SA=Yes were too young.*

Age ineligibility is more of concern for women who could become pregnant. For women only, the Sponsor performed an additional analysis at FDA request (see Appendix, Response to FDA Question 9/24/07 Table 4), finding that there were 220 women too young in the SA population of 391 women (56.3%), and that 29 out of the 220 women (13.2%) who were too young responded

SA=Yes. There were 101 women who responded SA=Yes, so of the women who responded SA=Yes, 29/101 (28.7%) were too young.

Of some concern is the prevalence for heart problem/disease, as shown for SA=Yes: here 33 subjects out of 68 with heart disease, or almost half, said the product was appropriate to use (SA=Yes). Also of concern is the prevalence for those already on medication to lower blood lipid, cholesterol, or triglycerides, again as shown for SA=Yes: 44 subjects out of 140 subjects on these medications (31.4%) said the product was appropriate to use.

The following results were found for the ineligibility criteria" pregnant or breastfeeding" and "may become pregnant". Of the 391 women in the SA population, there were 2 pregnant or breastfeeding, of whom none chose SA=Yes, and there were 12 who said "may become pregnant" of whom 1 chose SA=Yes. The numbers of women with these ineligibilities was, however, small.

Central to the LDL paradigm is the LDL value on which the subjects based their decisions. In the LDL-C arm, 52/122 (43%) of subjects who had LDL-C too high (above 170) still said SA = Yes, while 26/153 (17%) of subject whose LDL-C was too low (below 130) also selected SA = Yes. Similar results were found for PD = Yes.

MO Comment: *In the LDL-C arm, the highest prevalence ineligibility factors for SA=Yes were: heart problem/disease (48.5%);LDL-C is too high (42.6%); stroke (34.6%); diabetes (31.6%); medications to lower blood lipids, cholesterol or triglycerides (31.4%); HDL-C is too high (28.4%), taking other prescription medicines (25%), don't know LDL-C (22.4%). Those with heart disease, stroke, or diabetes should be followed by a physician, and their cholesterol levels should be treated aggressively. Mevacor should not be used with other lipid-lowering medication except under direction from a physician. The numbers of subjects on other listed prescription medications (potentially interacting drugs) was small in the SELECT study.*

Table 12 shows similar results for the Total-C arm, from Sponsor Table 11-20.

Table 12. Prevalence of Ineligibilities for the Total-C Arm

Total-C Paradigm	Prevalence (SA)[†]	SA=Yes[†]	Prevalence (PD)[†]	PD=Yes[†]
Ineligibility Criteria	N[‡] (%) (% of evaluators with criteria)	N (%) (% among those with criteria)	N (%) (% of evaluators with criteria)	N (%) (% among those with criteria)
Too young	281/743 (37.8)	41/281 (14.6)	281/744 (37.8)	37/281 (13.2)
Pregnant or breast-feeding[¶]	3/383 (0.8)	1/3 (33.3)	3/384 (0.8)	0/3 (0.0)
May become pregnant[¶]	10/383 (2.6)	1/10 (10.0)	10/384 (2.6)	0/10 (0.0)
Heart problem/disease	51/743 (6.9)	23/51 (45.1)	51/744 (6.9)	19\51 (37.3)
Stroke	20/743 (2.7)	6/20 (30.0)	20/744 (2.7)	5/20 (25.0)
Diabetes	56/743 (7.5)	17/56 (30.4)	56/744 (7.5)	14/56 (25.0)
Liver disease/liver problem	16/743 (2.2)	1/16 (6.3)	16/744 (2.2)	1/16 (6.3)
Allergic to the ingredient	7/742 (0.9)	0/7 (0.0)	7/743 (0.9)	0/7 (0.0)
Medication to lower blood lipid, cholesterol or triglycerides	121/742 (16.3)	42/121 (34.7)	121/743 (16.3)	31/121 (25.6)
Taking other listed prescription medicines	9/742 (1.2)	1/9 (11.1)	9/743 (1.2)	2/9 (22.2)
Don't know HDL-C number[‖¶]	147/367 (40.1)	24/147 (16.3)	148/377 (39.3)	22/148 (14.9)
HDL-C is too high[‖¶]	80/367 (21.8)	21/80 (26.3)	81/377 (21.5)	21/81 (25.9)

Don't know Total-C number‖	149/708 (21.0)	26/149 (17.4)	149/732 (20.4)	21/149 (14.1)
Total-C is too low‖	122/708 (17.2)	17/122 (13.9)	130/732 (17.8)	14/130 (10.8)
Total-C is too high‖	223/708 (31.5)	79/223 (35.4)	232/732 (31.7)	88/232 (37.9)
Drink large quantities of grapefruit juice	0/738 (0.0)	0/0 ( )	0/739 (0.0)	0/0 ( )
Used cholesterol numbers from non-fasted test	12/303§ (4.0)	4/12 (33.3)	12/304§ (3.9)	4/12 (33.3)
Don't have any of the listed risk factors¶	130/383 (33.9)	27/130 (20.8)	130/384 (33.9)	22/130 (16.9)

† Protocol violators are excluded.
‡ Excludes 1 participant with missing SA.
§ Fasting data is missing for 2 participants.
‖ Participants who were identified as having a procedural error which related to obtaining a cholesterol test and their SA or PD decisions were not included in respective decision categories.
¶ Eligibility questions were only asked to female participants.
PD = purchase decision; SA = self assessment.

MO Comment: *The format of Table 12 is the same as that of Table 11. There are 17 ineligibility criteria for the Total-C label. The first of these was "age too young" (again see MO Comment above), for which the prevalence is given in the second column (SA) as: there were 281 subjects too young, out of 743 who gave an SA response and an age, giving a proportion of 37.8%. The third column gives the corresponding prevalence of this ineligibility in those who said SA=Yes: 41 subjects out of 281 who were too young said SA=Yes, for a proportion 14.6%. From Sponsor Table 11-18 (see Appendix), there were 259 subjects who responded SA=Yes, so 41/259 (15.8%) of subjects who said SA=Yes were too young.*

Age ineligibility is more of concern for women who could become pregnant. For women only, the Sponsor performed an additional analysis at FDA request (see Appendix, Response to FDA Question 9/24/07 Table A6), finding that there were 195 women too young in the SA population of 383 women (50.9%), and that 22 out of the 195 women (11.3%) who were too young responded SA=Yes. There were 106 women who responded SA=Yes, so of the women who responded SA=Yes, 22/106 (20.8%) were too young.

Of some concern is the prevalence for heart problem/disease, as shown for SA=Yes: here 23 subjects out of 51 with heart disease, or almost half, said the product was appropriate to use (SA=Yes). Also of concern is the prevalence for those already on medication to lower blood lipid, cholesterol, or triglycerides, again as shown for SA=Yes: 42 subjects out of 121 subjects on these medications (34.7%) said the product was appropriate to use.

The following results were found for the ineligibility criteria" pregnant or breastfeeding" and "may become pregnant". Of the 383 women in the SA population, there were 3 pregnant or breastfeeding, of whom 1 chose SA=Yes, and there were 10 who said "may become pregnant" of whom 1 chose SA=Yes. The numbers of women with these ineligibilities was, however, small.

MO Comment: *In the Total-C arm, the highest prevalence ineligibility factors for SA=Yes were: heart problem/disease (48.5%); medications to lower blood lipids, cholesterol or triglycerides (34.7%), diabetes (30.4%); stroke (30%); total-C too high (35.4%); HDL-C too high (26.3%); don't know HDL-C (16.3%); don't now Total-C (17.4%). Those with heart disease, stroke, diabetes should be followed by a physician and their cholesterol levels should be treated aggressively. Mevacor should not be used with another statin, which increases the chance of myopathy/rhabdomyolysis, and it should not be used with other lipid-lowering medication except under direction from a physician. The numbers of subjects on other listed prescription medications (potentially interacting drugs) was small in the SELECT study.*

MO Comment: *Efficacy results* (Figure 2, Figure 3, Figure 4, Figure 5) *were similar for the two arms in terms of proportion completely correct, which was about 20% in either label paradigm for either SA=Yes or PD=Yes. The most prevalent ineligibilities in Table 11 and Table 12 were likewise similar in the two arms, most importantly related to presence of heart disease, diabetes, stroke, and medications to lower blood lipids, cholesterol or triglycerides.*

In addition, the proportions of subjects who selected SA=Yes without knowing required cholesterol numbers was similar in the two arms, although in the total SA populations there were significantly more subjects who did not know their LDL-C than those who did not know their total C. In the LDL-C arm, 268/714 (37.5%) did not know their LDL-C, but only 60/268 (22.4%) selected SA=Yes. In the Total-C arm, 149/708 (21%) did not know their Total-C, but 26/149 (17.4%) selected SA=Yes.

The ineligibility due to other lipid-lowering medications was also similarly prevalent, over 30%, in both arms for SA=Yes. Age too young is less prevalent (about 15%) in both arms for SA=Yes. The prevalence of the ineligibility pregnant/ breast feeding/may become pregnant for SA=Yes was about 10% in both arms, with small numbers in the samples. Actually pregnant or breastfeeding subjects numbered only 2 in the LDL-C arm and 3 in the Total-C arm, and 1 subject in the Total-C arm said SA=Yes (this subject was mitigated and the reviewer concurs).

All of the above analyses discuss the numbers of participants with a specific ineligibility who selected SA=Yes incorrectly, but the prevalences can be presented a second way. The prevalences of the specific ineligibilities within the total population who said SA=Yes are shown in Sponsor Tables 11-17 and 11-18 of the Appendix. In the entire population of participants who said SA=Yes, the most common ineligibilities were age, not knowing HDL-C or LDL-C, having lipid values out of range, and not having one additional CHD risk factor.

Calculated 10-Year Risk for Hard CHD. Participants were not required to calculate their 10-year risk score for "Hard CHD" (myocardial infarction and coronary death) to make their SA and PD. However, the Hard CHD risk of all participants was calculated by the Sponsor 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-C, HDL-C, and blood pressure were used for the calculation along with the participant's self-reported values for age and smoking status. The differences between label paradigms and SA and PD are not meaningful.

Table 13. Calculated 10-year Hard CHD Risk for SA=Yes, in LDL-C Arm

10-year Hard CHD Risk[†]	Number of Self-Reported CHD Factors						Total[§]	
	0	1	2	3	4	5	n	%
Men								
Unknown	0	2	1	1	0	0	4	3.2
Undefined (Age >79 Years)	0	0	0	0	0	0	0	0.0
<5%	0	7	5	1	0	0	13	10.5
5 to <10%	0	4	6	4	0	0	14	11.3
10 to 20%	0	7	12	15	3	0	37	29.8
>20 to 25%	0	1	0	4	2	0	7	5.6
>25%	0	0	1	2	3	0	6	4.8
CHD, Diabetes or Stroke[‡]	0	2	6	6	2	0	16	12.9
Taking Rx Cholesterol Medication	0	2	8	12	5	0	27	21.8
Sub-Total	0	25	39	45	15	0	124	
Women								
Unknown	0	0	0	0	0	0	0	0.0
Undefined (Age >79 Years)	0	1	0	0	0	0	1	1.1
<5%	2	17	20	3	0	0	42	46.7
5 to <10%	0	4	10	5	0	0	19	21.1
10 to 20%	0	1	0	2	0	0	3	3.3
>20 to 25%	0	0	0	0	0	0	0	0.0
>25%	0	0	1	0	0	0	1	1.1
CHD, Diabetes or Stroke[‡]	0	0	5	6	1	0	12	13.3
Taking Rx Cholesterol Medication	0	4	3	3	2	0	12	13.3
Sub-Total	2	27	39	19	3	0	90	
All Users								
Unknown	0	2	1	1	0	0	4	1.9
Undefined (Age >79 Years)	0	1	0	0	0	0	1	0.5
<5%	2	24	25	4	0	0	55	25.7
5 to <10%	0	8	16	9	0	0	33	15.4
10 to 20%	0	8	12	17	3	0	40	18.7
>20 to 25%	0	1	0	4	2	0	7	3.3
>25%	0	0	2	2	3	0	7	3.3
CHD, Diabetes or Stroke[‡]	0	2	11	12	3	0	28	13.1
Taking Rx Cholesterol Medication	0	6	11	15	7	0	39	18.2
Total	2	52	78	64	18	0	214	

[†] Based on Framingham Risk Assessment Tool from NCEP ATPIII.
[‡] Secondary Prevention/CHD Risk Equivalent.
[§] Participants with missing data, participants whose eligibility could not be determined due to a data collection issue and protocol violators were excluded.
SA=self assessment.

MO Comment: *These CHD risk assessments were based on measured lipid values during the study period and used the Framingham 10-year CHD risk tables. The men who selected SA=Yes in the LDL-C arm tended to have higher CHD risk than the women. Approximately 41% of the men with SA=Yes fell in the 5% to 20% CHD risk range compared with approximately 25% of the women falling in this range. A little over 10% of men who responded SA=Yes had <5% CHD risk, but 46.7% of the women with SA=Yes had <5% CHD risk. The proportion of subjects with CHD, diabetes or stroke who said SA=Yes was about the same, about 13%, for both men and women.*

Table 14. Calculated 10-year "Hard" CHD risk, for SA=Yes in Total-C Arm

10-year Hard CHD Risk[†]	Number of Self-Reported CHD Factors						Total[§]	
	0	1	2	3	4	5	n	%
Men								
Unknown	0	3	0	1	1	0	5	3.4
Undefined (Age >79 Years)	0	0	0	0	0	0	0	0.0
<5%	4	7	5	1	0	0	17	11.7
5 to <10%	1	15	7	3	0	0	26	17.9
10 to 20%	0	17	23	11	2	0	53	36.6
>20 to 25%	0	0	0	5	1	0	6	4.1
>25%	0	0	1	1	0	0	2	1.4
CHD, Diabetes or Stroke[‡]	0	3	4	4	3	1	15	10.3
Taking Rx Cholesterol Medication	1	3	12	4	1	0	21	14.5
Sub-Total	6	48	52	30	8	1	145	
Women								
Unknown	1	0	0	1	0	0	2	2.1
Undefined (Age >79 Years)	0	1	1	0	0	0	2	2.1
<5%	4	13	21	3	0	0	41	42.3
5 to <10%	0	5	6	6	0	0	17	17.5
10 to 20%	0	0	3	2	2	0	7	7.2
>20 to 25%	0	0	0	0	0	0	0	0.0
>25%	0	0	1	0	1	0	2	2.1
CHD, Diabetes or Stroke[‡]	0	2	5	3	0	0	10	10.3
Taking Rx Cholesterol Medication	0	4	10	2	0	0	16	16.5
Sub-Total	5	25	47	17	3	0	97	
All Users								
Unknown	1	3	0	2	1	0	7	2.9
Undefined (Age >79 Years)	0	1	1	0	0	0	2	0.8
<5%	8	20	26	4	0	0	58	24.0
5 to <10%	1	20	13	9	0	0	43	17.8
10 to 20%	0	17	26	13	4	0	60	24.8
>20 to 25%	0	0	0	5	1	0	6	2.5
>25%	0	0	2	1	1	0	4	1.7
CHD, Diabetes or Stroke[‡]	0	5	9	7	3	1	25	10.3
Taking Rx Cholesterol Medication	1	7	22	6	1	0	37	15.3
Total	11	73	99	47	11	1	242	

[†] Based on Framingham Risk Assessment Tool from NCEP ATPIII.
[‡] Secondary Prevention/CHD Risk Equivalent.
[§] Participants with missing data, participants whose eligibility could not be determined due to a data collection issue and protocol violators were excluded.
SA=self assessment.

MO Comment: *These CHD risk assessments were based on measured lipid values during the study period and used the Framingham 10-year CHD risk tables. The men who selected SA=Yes in the Total-C arm tended to have higher CHD risk than the women. Approximately 55% of the men with SA=Yes fell in the 5% to 20% CHD risk range compared with approximately 25% of the women falling in this range. About 12% of men with SA=Yes had <5% CHD risk, but 42.3% of the women with SA=Yes had <5% CHD risk. The proportion of subjects with CHD, diabetes or stroke who said SA=Yes was about the same, about 10%, for both men and women.*

It is not clear why the SA population for women is 90 in Table 13 *but is 101 in Table A4 in the Appendix. Likewise the SA population for women is 97 in* Table 14 *but is 106 in Table A6.*

The CHD risk profiles of subjects who selected SA=Yes in the two study arms were not significantly different. Fewer than half the subjects (34.1% in the LDL-C arm, 42.6% in the Total-C arm) in either study arm had Framingham CHD risk of 5% to 20%, the range targeted by the Sponsor for treatment. Over 40% of women who responded SA=Yes in both study arms had low CHD risk <5%. In addition, about 15- 20% of subjects in both study arms (men and women combined) who said SA=Yes had >20% CHD risk or had CHD, diabetes or stroke. Also, in both study arms, more than 15% of subjects with SA=Yes were taking prescription cholesterol medications.

Specific Areas of Focus

This section will discuss additional areas of interest including deficiencies which are mentioned in the non-approval letter of 2/23/05:

- Women < 55 years
- Women of child-bearing potential
- Liver disease
- Interacting medications
- Lipid-lowering medications

Women < 55 years of Age. According to the Sponsor, a small percentage of women <55 years who evaluated the product made incorrect self-assessment (11.1%, 42/377) or purchase decisions (12.4%, 48/387). This is an improvement (approximately 50%) over CUSTOM. Additionally, of those 42 women who made an incorrect self-assessment decision in SELECT, 50% were within 4 years of age 55. Of the 48 women <55 years of age who made an incorrect purchase decision in SELECT, 44% were within 4 years of age 55. In comparison to CUSTOM where 37% (161/430) of the female user population were women <55 years of age, in SELECT 25.5% (48/188) of the females who made a positive purchase decision were <55 years of age.

MO Comment: *FDA attempted to reproduce these results from analysis of Sponsor Tables 10-8 and 10-9 (see Appendix) and found similar but different results. The total number of women under age 55 with PD=Yes, both arms combined, was 416, and a total of 55 (13.2%) women under 55 years said PD=Yes. Of the 188 women who said PD=Yes (all ages, both arms), there were 55 (29%) who were <55 years old.*

A total of 21 women under age 50 said SA=Yes in the two arms combined. The ages of these women were: {19, 21, 24, 33, 34(x2), 35, 38, 42, 43, 44, 45, 46, 47(x2), 48(x2), 49(x4)}. Of these, 9 said they would talk to a doctor, and 3 said they were told by a doctor to be treated for cholesterol.

Of the women of age < 54 in the study who made a positive self-assessment decision, 21 (50%) of the 42 women < 54 were between the ages of 50-53. Eighteen (42.9%) of these women were within range for LDL-C and 20 (47.6%) were within range for Total-C. Thirty-five (83.3%) of the women had ≥1 risk factor. Twenty (47.6%) of these women had ≥ 2 risk factors.

Pregnant/Breastfeeding/Child bearing Potential. Four participants in the total study population stated that they were pregnant. Three of these women correctly stated that the product is not appropriate for them and that they do not wish to purchase. However, one of these participants (012-5988-82558) stated that she was appropriate for the product but decided not to purchase MEVACOR™ Daily. The investigator felt that this participant did not understand the SA question. The participant stated that she thought the question was asking whether she would "use the product later on" and whether "it was good or bad for her to use." She acknowledged that she did not meet the eligibility requirements on the label and said that her answer to the self-assessment question would be "no" after she understood the question more fully.

One study participant stated that she was breast-feeding. She correctly stated that the product is not appropriate for her, and that she did not wish to purchase. Twenty-two females stated that they may become pregnant. Of these participants, none of them decided to purchase the product. However, two participants (003-1473-82933 and 001-3596-81737) stated that they were appropriate for the product. The sponsor mitigated both subjects on the basis of their open-ended responses.

MO Comment: *We do not agree that Subject 001-3596-81737 can be mitigated. This subject in the Total-C arm was a 38 year old female who said SA=Yes but was ineligible to use for multiple reasons: age too young, may become pregnant, and did not know HDL or total-C. The reason given for not purchasing the product was that it was too expensive. She could not explain why she said SA=Yes. Upon further questioning by the investigator and re-reading the package, this subject did eventually state that the product was not appropriate for her to use, but she came to this realization after prompting by the investigator and therefore should not be mitigated.*

We also consider the mitigation of 003-1473-82933 to be debatable. This subject was a 34 year old female with Total-C 200-240 and LDL > 171, who did not know her HDL. She said PD=No and wanted to talk to a doctor. She was not currently planning to become pregnant but might do so within the next 2 years. Follow-up questioning (after she was informed that her SA=Yes response was incorrect) revealed she would like to ask her doctor about alternative medications she could take in the event that she becomes pregnant. When asked what the self-assessment question meant, she thought it was whether she would buy and use the product, rather than whether she met the criteria. Subject said she didn't notice the information on label and did not read the label thoroughly. This subject's inconsistent answers exemplify the problems inherent in a self-selection study, as opposed to an actual use study, for determining how and whether a given subject would use the product. The more conservative approach would be not to mitigate and to accept the subject's original answers at face value.

Hence of the 22 women in the study who may become pregnant, two subjects said SA=Yes of whom one (or neither) can be mitigated. The one subject (012-5988-82558) who said she was pregnant, and said SA=Yes, was age 52 (she also stated she ***may*** *be pregnant at a later point in the interview) and was low literate. Only 4 pregnant subjects were enrolled. It is difficult to extrapolate these results to women of childbearing age, because of the small sample size. Moreover, procedure of asking a women if she " thinks she may become pregnant" may underestimate the potential for use by pregnant women, since many pregnancies are unintended.*

Liver disease. The SELECT study enrolled subjects with liver disease or liver problems. There were 39/1495 (2.6%) participants in the study who evaluated SA, and 39/1494 (2.6%) participants who evaluated for PD, who indicated that they had liver disease or liver problems. Of the participants with

liver disease, 3 (7.7%) responded yes to the SA question and 3 (7.7%) responded yes to the PD question.

Interacting medications. The SELECT study enrolled a small sample of subjects on potentially interacting medications. Specifically, 21/1493 (1.4%) of the participants who evaluated for SA and 21/1494 (1.4%) of the participants who evaluated for PD in SELECT were taking potentially interacting medication. Four (19.1%) of the participants who were taking interacting medication responded yes to SA and 3 (14.3%) of the participants who were taking interacting medication said yes to PD. Of the 4 participants who felt they were appropriate despite the fact that they were taking potentially interacting medications, all of them said that they would talk to their doctor and one of them displayed evidence of not understanding the SA question.

In the LDL-C paradigm, three participants with SA = Yes were taking potentially interacting medicines. Each of the following medications was taken by one participant: amiodarone, verapamil, and cyclosporine. One participant with a positive purchase decision was taking verapamil. In the Total-C paradigm, one participant with a positive self-assessment decision was taking clarithromycin. Two participants with a positive purchase decision were taking potentially interacting Medications; one was taking clarithromycin and one was taking ketoconazole.

MO Comment: *The sample of subjects taking potentially interacting medications is small. The statistics refer to the two study arms combined.*

Lipid-lowering medications. The Sponsor determined the prevalence of the entire population of participants who were taking lipid-lowering medications. Of the participants in SELECT who evaluated for SA (both study arms combined), 261/1492 (17.5%) were taking lipid-lowering medication. Similarly, of the participants who evaluated for PD, 259/1491 (17.4%) were taking lipid-lowering medication. From the results in Table 11 and Table 12 for the two study arms combined, 86 (33.0%) of the participants taking lipid-lowering medication stated that they were appropriate to use the product, and 58 (22.4%) decided that they would like to purchase the product. Similarly, in CUSTOM, 29.8% (213/714) of Evaluators who were using lipid-lowering medication decided to purchase the product.

MO Comment: *The SELECT results show that 20% to 30% of consumers already on prescription lipid-lowering medications will select to use OTC Mevacor. It is not clear why the denominators for interacting medications and for lipid-lowering medications are different.*

Reasons for Incorrect Responses. This section will present the reasons why subjects gave incorrect SA=Yes and PD=Yes responses. The rest of this review will focus on the SA decision since purchase decisions can be influenced by other factors such as cost.

Ineligible subjects who responded SA=Yes were later asked the following question:

> *"According to the questions you answered about your medical history and personal characteristics, MEVACOR™ Daily is not appropriate for you. Yet, earlier you said that this product is appropriate for you to use. I would like to explore this issue a little bit more with you, because it will help us improve the information on the label. As best as you can, please tell me why you thought MEVACOR™ Daily was appropriate for you to use even though (reasons (s) for ineligibility were pre-filled by the computer-generated script)?"*

The investigator asked the participant this question for up to four reasons for ineligibility. The Sponsor classified these responses into pre-determined phrases.

Participants who responded PD=Yes, but SA=No, were asked the following question before completing the Eligibility Assessment (EA):

> *"Earlier, you mentioned that the product is not appropriate for you to use. Which of the requirements don't you meet?"* (Eligibility criteria were not shown or read to the participants). After the EA, these same participants were asked the following questions:
> *"Earlier, you said that this product is not appropriate for you to use. Yet, you also said that you want to buy this product right now. I would like to explore this issue a little bit more with you, because it will help us improve the information on the label. As best as you can, please tell me your thoughts when you decided that you want to buy this product even though you recognize that it is not appropriate for you to use because…?"*

All reasons that the participants listed in the previous question were pre-filled by the system into this question. Responses were classified into predetermined phrases.

Summaries follow of reasons given by participants for incorrect SA for individual label criteria.

Table 15 shows the frequency of reasons given by participants who chose SA=Yes but who were incorrect because their age was too young.

Table 15. Why you thought MEVACOR™ Daily was Appropriate for You to Use Even Though You Are Too Young

Provided Response[†]	LDL Paradigm(N=52)[‡§]	Total C Paradigm(N=50)[‡‖]	Total(N=102)
Age is close	14	15	29
Want to lower my cholesterol	10	11	21
Family history	13	6	19
Desire to lower cholesterol outweighs characteristic	8	6	14
Previously taken this type of medication	7	4	11
Cholesterol is high	5	5	10
Concerned with risk of heart attack	6	4	10
I know my numbers are bad/high	3	3	6
Less expensive than prescription medication	4	0	4
Doctor told me cholesterol is bad	1	3	4
No reason provided	2	2	4
Doctor told me to take cholesterol medication	3	1	4
Planning to talk to doctor	3	0	3
Want to improve health	1	2	3
Did not notice information on label	2	1	3
Meets other criteria	2	1	3
Total in right range	0	2	2
Misunderstood information in label	0	2	2
Want to live longer	0	2	2
Want to keep my cholesterol low/good	0	1	1
LDL in right range	1	0	1
Other Specify	5	4	9

[†] Participants could have provided up to 3 reasons for appropriateness.
[‡] Number of participants who provided a response to the question are included Protocol violators are excluded.
[§] Eleven participants provided reasons that were not considered ineligible for age as per data summarization plan (10 Males 44 years of age and 1 Female 54 years of age).
[‖] Ten participants provided reasons that were not considered ineligible for age as per data summarization plan (8 Males 44 years of age and 2 Female 54 years of age).

MO Comment: *The most common reason was "age is close". The majority of participants who selected SA=Yes were within 5 years of the label eligibility criterion. Two of the top four reasons involved a desire to lower cholesterol. Family history was the third most frequently cited reason.*

Table 16 summarizes the frequency of reasons given by participants for selecting SA=Yes but who were incorrect because they were already taking lipid-lowering medications.

Table 16. Why you thought MEVACOR™ Daily was Appropriate for You to Use Even Though You Are Taking Lipid Lowering Medications?

Provided Response[†]	LDL Paradigm(N=41)[‡]	Total C Paradigm(N=42)[‡]	Total(N=83)
Take in place of current medication	10	17	27
Less expensive then prescription medication	8	8	16
Previously taken this type of medication	3	6	9
Planning to talk to doctor	4	4	8
Want to lower my cholesterol	3	2	5
Meets other criteria	2	3	5
Concerned with risk of heart attack	1	3	4
Clinical study	2	2	4
Family history	0	2	2
Want to improve health	2	0	2
Numbers low because of current medication	1	1	2
No reason provided	2	0	2
Doctor told me to take cholesterol medication	2	0	2
Medication does not interact	1	0	1
Had condition in past/not currently	1	0	1
Did not notice information on label	0	1	1
Desire to lower cholesterol outweighs characteristic	1	0	1
Other Specify	10	8	18

[†] Participants could have provided up to 3 reasons for appropriateness.
[‡] Number of participants who provided a response to the question are included. Protocol violators are excluded.

MO Comment: *The most frequent reasons for choosing SA=Yes, even though the subject was already taking lipid-lowering medication, were to replace the prescription medication or specifically to replace it because of lower cost (these reasons were separated by the Sponsor). About half of participants ineligible because they were on prescription lipid-lowering medications chose SA=Yes because they wanted to replace the prescription medication.*

Examples follow of verbatim statements from subjects who chose SA=Yes despite already taking prescription lipid-lowering medications:

- Because I thought it would help my cholesterol to take both. My doctor has had me on both Zocor and Tricor at the same time in the past So I see no reason not to take Zocor and Mevacor at the same time
- I figured anything is going to be a help. I've been fighting cholesterol for 2 years—cholesterol level of 300
- Have not been taking my Crestor for two weeks because I ran out. It still costs too much even with insurance. I also wanted to see what my cholesterol numbers are without medicine.
- I am currently using Zocar, but I would like to try a non-prescription medication. I think it would give me better control of my health.
- I have been taking cholesterol medication for a couple of years and nothing seems to work, so I am willing try something new to help myself
- My heart doctor wants me on 2 cholesterol I am on Zetia medication and I need another to go along with it
- I would like to switch to an over the counter so that I can see the doctor less and pay less money
- Would stop taking Lipitor if decided to take Mevacor daily
- Would use this instead of Crestor
- Tricor that patient is taking is not lowering lab results they are only going up.
- Would like an OTC which may work better than Tricor or could replace Tricor.
- Thought it would be something better to lower my LDL, because the drug I am on does not lower my cholesterol enough. And I diet and exercise and still have high cholesterol
- Thinks maybe it is as good as what he is on, cost ok, and won't have to see the Dr.

Table 17 and Table 18 display the counts of specific lipid-lowering medications being taken by participants who said SA=Yes or PD=Yes. Atorvastatin, simvastatin, and lovastatin were the most commonly taken cholesterol-lowering medications.

Table 17. Lipid-Lowering Medicines: LDL-C Arm

Cholesterol/Lipid Lowering Medicines	SA=Yes (N = 44)[†]	PD=Yes (N = 27)[†]
Atorvastatin	12	8
Atorvastatin and gemfibrozil	1	0
Ezetimibe	3	2
Ezetimibe and atorvastatin	1	1
Ezetimibe/simvastatin	2	1
Fenofibrate	3	1
Fluvastatin	1	0
Gemfibrozil	1	0
Lovastatin	7	2
Lovastatin/niacin	2	2
Niacin	1	0
Rosuvastatin calcium	2	3
Simvastatin	8	7

[†]Protocol violators are excluded.
PD = Purchase Decision; SA = Self Assessment.

MO Comment: *Atorvastatin and simvastatin are more potent than lovastatin, so subjects may not be adequately treated if they substitute an OTC statin. Ezetimide, fibrates, and niacin have different mechanisms of action. These medications should not be freely substituted by statins.*

Table 18. Lipid-Lowering Medicines: Total-C Arm

Cholesterol/Lipid Lowering Medicines	SA=Yes (N = 41)[†,‡]	PD=Yes (N = 31)[†]
Atorvastatin	14	12
Atorvastatin and niacin	1	0
Ezetimibe	3	1
Ezetimibe and niacin	1	1
Ezetimibe/simvastatin	3	2
Ezetimibe/simvastatin and fenofibrate	1	1
Fluvastatin	1	1
Lovastatin	6	4
Rosuvastatin calcium	3	3
Simvastatin	7	5
Simvastatin and fenofibrate and gemfibrozil	1	1

[†]Protocol violators are excluded
[‡]One additional participant, who said SA=Yes, was counted as ineligible for criteria Taking Cholesterol/Lipid Lowering Medicines even though he did not know which medications he was taking.
PD = Purchase Decision; SA = Self Assessment.

MO Comment: *The specific lipid-lowering medications being taken by participants who said SA=Yes or PD=Yes are similar in the two study arms.*

Participants who had decided to buy MEVACOR™ Daily and reported that they were taking a lipid lowering medication were asked the following question:

"You mentioned that you are currently taking a prescription medicine for your cholesterol but that you still want to buy MEVACOR™ Daily. You may have already mentioned this, but do you plan to take MEVACOR™ Daily along with your prescription medicine or in place of it?"

Table 19 summarizes the responses, in which the majority of participants said that they would take OTC Mevacor Daily in place of their current lipid-lowering medication.

Table 19. Plans to take Mevacor Daily Along With, or In Place Of, Prescription Medications

Reported Action	LDL-C Paradigm (N=27) N (%)	Total-C Paradigm (N=31) N (%)
Take along with it	8 (29.6%)	8 (25.8%)
Take in place	14 (51.9%)	18 (58.1%)
Don't know	1 (3.7%)	2 (6.5%)
Other	3 (11.1%)	3 (9.7%)
Missing	1 (3.7%)	0 (0.0%)

MO Comment: *A majority of participants who responded to this question stated that they would take OTC lovastatin in place of their current lipid-lowering medication. In addition, almost 30% of subjects stated they would take Mevacor along with their current medication. Taking two statins together, or taking a statin with another lipid-lowering drug, may increase the risk of myopathy/rhabdomyolysis from high levels of plasma HMG-CoA reductase inhibitory activity.*

Table 20 provides more information on the participants who said PD=Yes but were taking a prescription medication to lower blood lipids, cholesterol, or triglycerides. For example, eight participants in the LDL-C paradigm said they would take it along with their prescription cholesterol medicine, but of these eight, one wanted to talk with a doctor, and five had a history of diabetes, stroke or heart disease.

Table 20. Subjects who Decided PD=Yes, but were on Lipid-Lowering Medications

Reported Action	LDL-C Paradigm (N=27)† N (%)	Talk to Doctor N	Diabetes, Stroke or Heart Disease N	Total-C Paradigm (N=31)† N (%)	Talk to Doctor N	Diabetes, Stroke or Heart Disease N
Take along with it	8 (29.6%)	1	5	8 (25.8%)	3	7
Take in place	14 (51.9%)	5	1	18 (58.1%)	5	6
Don't know	1 (3.7%)	1	1	2 (6.5%)	1	0
Other	3 (11.1%)	3	1	3 (9.7%)	2	2
Missing	1 (3.7%)	1	0	0 (0.0%)	0	0
† Protocol violators are excluded.						

MO Comment: *Of the 16 subjects (eight in each arm) who responded that they would take Mevacor Daily in addition to their cholesterol lowering medication), one subject in the LDL arm and three in the Total-C arm would talk to their doctor. The majority of these individuals had*

high CHD risk. For these subjects, the risk of myopathy/ rhabdomyolysis would be increased, and moreover these subjects should be aggressively treated for their elevated lipids under medical supervision, rather than switching to OTC therapy.

Of the 32 subjects who would take Mevacor Daily in place of their prescription medication (14 in the LDL-C arm, 18 in the Total-C arm) there were five in each study arm who would talk to a doctor.

Table 21 gives additional information on participants with CHD, diabetes, or stroke who said SA=Yes or PD=Yes. On average approximately 30% of participants with CHD, diabetes, or stroke wanted to purchase MEVACOR™ Daily. The proportions are similar for participants who said yes for SA and PD in the LDL-C and Total-C paradigms. Approximately two-thirds of participants who reported CHD, diabetes, or stroke were not taking any lipid lowering medications.

Table 21. Participants With CHD, Diabetes, or Stroke; LDL-C Arm

	Participants[†]	Taking Rx Cholesterol Medicine[‡]	Taking Rx Cholesterol Medicine and would Talk to Dr
CHD			
SA=Yes	32	17	10
PD=Yes	22	8	3
DIABETES			
SA=Yes	24	9	7
PD=Yes	15	5	3
STROKE			
SA=Yes	8	4	3
PD=Yes	7	2	1
Total Unique Participants			
SA=Yes	45	17	10
PD=Yes	33	8	3

[†] Excludes protocol violators, participants with cholesterol test after PD and before EA, participants with cholesterol test after SA, and participants with missing data.
[‡] Excludes participants who do not know whether they are taking an Rx cholesterol medicine.
ED = eligibility assessment; PD = purchase decision; SA = self assessment.

MO Comment: *In the LDL-C arm, there were 17/45(38%) unique participants with CHD, diabetes, or stroke, who said SA=Yes and who were taking prescription cholesterol medications. Of these individuals taking cholesterol medications, 10/17 (59%) would consult with their doctor. For the purchase decision in the LDL-C arm, there were 8/33 (24%) unique participants with CHD, diabetes, or stroke, who said PD=Yes and who were taking prescription cholesterol medications. Of these individuals taking cholesterol medications, 3/8 (38%) would consult with their doctor. The total number of subjects with CHD was 68, the number of subjects with diabetes was 79, and the number of subjects with stroke was 26; some subjects reported more than one of these conditions (see Table 11).*

Table 22 shows similar statistics for the Total-C arm.

Table 22. Participants With CHD, Diabetes, or Stroke; Total-C Arm

	Participants†	Taking Rx Cholesterol Medicine‡	Taking Rx Cholesterol Medicine and would Talk to Dr
CHD			
SA=Yes	20	8	4
PD=Yes	17	7	3
DIABETES			
SA=Yes	17	6	4
PD=Yes	14	5	3
STROKE			
SA=Yes	6	4	2
PD=Yes	5	4	2
Total Unique Participants			
SA=Yes	40	15	9
PD=Yes	34	14	8

† Excludes protocol violators, participants with cholesterol test after PD and before EA, participants with cholesterol test after SA, and participants with missing data.
‡ Excludes participants who do not know whether they are taking an Rx cholesterol medicine.
EA = eligibility assessment; PD = purchase decision; SA = self assessment.

MO Comment: *In the Total-C arm, there were 15/40 (38%) unique participants with CHD, diabetes, or stroke, who said SA=Yes and who were taking prescription cholesterol medications. Of these individuals taking cholesterol medications, 9/15 (60%) would consult with their doctor. For the purchase decision in the Total-C arm, there were 14/34 (41%) unique participants with CHD, diabetes, or stroke, who said PD=Yes and who were taking prescription cholesterol medications. Of these individuals taking cholesterol medications, 8/14 (57%) would consult with their doctor. There were, from Table 12, 51 subjects with CHD in the Total-C arm, 20 subjects with stroke, and 56 subjects with diabetes, where some subjects had more than one of these conditions.*

Participants who were not currently using a prescription medicine to lower cholesterol at the time of their study visit were asked 1) if they ever talked to a doctor about using prescription medicine to lower cholesterol, 2) if they ever took a prescription medicine to lower cholesterol, 3) why they were no longer taking the prescription cholesterol-lowering medicine, and 4) why they were interested in non-prescription medicine instead of prescription for their cholesterol. Results of these questions are summarized in Table 23, Table 24, and Table 25.

Differences were noted between participants who said SA or PD Yes and those who said SA or PD No. A much larger percentage of participants who said SA or PD Yes reported that they had talked to a doctor about using prescription cholesterol medicine than those who said SA or PD No. A similar result was observed for participants who had previously taken a prescription cholesterol medicine. These results suggest that some participants may have chosen SA=Yes or PD=Yes because their doctor had discussed taking cholesterol-lowering medicine with them.

Table 23. Subjects not on Prescription Medications, Two Arms Combined, N=1226

	SA=Yes N=406		SA=No N=749		PD=Yes N=371		PD=No N=855	
	n	%	n	%	n	%	n	%
Have you ever talked with a doctor about using a prescription medicine for your cholesterol?								
Yes	240	59.1	292	39.0	246	66.3	325	38.0
No	164	40.4	456	60.9	123	33.2	529	61.9
Don't have a doctor that treats cholesterol-related problems	2	0.5	1	0.1	2	0.5	1	0.1
Have you ever taken a prescription medicine for your cholesterol?								
Yes	160	39.6	170	22.7	171	46.3	193	22.6
No	243	60.1	576	77.0	198	53.7	658	77.0
Don't know	1	0.2	2	0.3	0	0.0	3	0.4
Did you talk to your doctor about stopping your prescription cholesterol medicine or not?								
Yes	57	35.6	85	50.0	62	36.3	94	48.7
No	103	64.4	85	50.0	109	63.7	99	51.3

† 1226 includes 71 SA=Other which are not displayed due to small numbers.
PD = purchase decision; SA = self assessment.

MO Comment: *In the two study arms combined, there were 1226 subjects not on lipid-lowering medications out of a total of 1499 who completed the study. Subjects were much more likely to select SA=Yes or PD=Yes if they had talked to a doctor about using a prescription cholesterol medication or if they had previously taken a prescription medication. They were also more likely to say SA=Yes or PD=Yes if they had not talked to a doctor about stopping their cholesterol medication.*

Table 24. Reasons for Stopping Prescription Medication, Two Arms Combined, Most Common Responses ≥10%, N=365

Reasons why no longer taking a prescription cholesterol medicine (Classified Responses)	SA=Yes N=160‡		SA=No N=170‡		PD=Yes N=171‡		PD=No N=193‡	
	n	%	n	%	n	%	n	%
Side effects	48	30.0	60	35.3	53	31.0	70	36.3
Too expensive	47	29.4	33	19.4	52	30.4	33	17.1
Do not have insurance	31	19.4	22	12.9	33	19.3	20	10.4
Didn't go back to doctor	14	8.8	14	8.2	18	10.5	13	6.7

† 365 includes 35 SA=Other which are not displayed due to small numbers.
‡ Participants could have provided up to 3 reasons.
PD = purchase decision; SA = self assessment.

MO Comment: *The most frequent reasons for stopping prescription cholesterol medications were side effects, too expensive, and do not have insurance. The subjects for whom cost was apparently an issue, who gave as reasons "too expensive" and "do not have insurance", were*

more likely to select SA=Yes and PD=Yes. For PD Yes and PD no combined, there were 123 subjects who discontinued and gave side effects as a reason, out of 364 (34%).

Table 25. Reasons for Preferring OTC Medication, Two Arms Combined, Most Common Responses ≥10%, N=1226

Reasons why interested in exploring non-prescription medicine rather than prescription medicine for cholesterol (Classified Responses)	SA=Yes N=406‡		SA=No N=749‡		PD=Yes N=371‡		PD=No N=855‡	
	n	%	n	%	n	%	n	%
Less expensive	202	49.8	317	42.3	192	51.8	356	41.6
Convenience	117	28.8	242	32.3	100	27.0	274	32.0
Don't have to go to doctor	62	15.3	117	15.6	59	15.9	128	15.0
Feels safer (less side effects)	46	11.3	88	11.7	44	11.9	97	11.3
Cholesterol test	15	3.7	78	10.4	10	2.7	89	10.4
Don't have insurance	33	8.1	44	5.9	37	10.0	44	5.1
† 1226 includes 71 SA=Other which are not displayed due to small numbers. ‡ Participants could have provided up to 3 reasons. PD = purchase decision; SA = self assessment.								

MO Comment: *The reasons given for preferring OTC cholesterol medication were lower cost, convenience, don't have to go to a doctor, and feels safer (less side effects).*

Table 26 shows that approximately 30% of the participants reported having no health insurance. In addition, approximately 10% of the participants who have health insurance indicated that their health insurance did not pay anything for prescriptions. The responses regarding health insurance and prescription coverage were similar across SA and PD Yes and No decisions.

Table 26. Health Insurance Coverage, Two Arms Combined, N=1489

	SA=Yes N=491		SA=No N=912		PD=Yes N=428		PD=No N=1060	
	n	%	n	%	n	%	n	%
Don't have health insurance	154	31.4	275	30.2	138	32.2	312	29.4
Have health insurance	337	68.6	637	69.8	290	67.8	748	70.6
Insurance pays for prescriptions	295	87.5	573	90.0	248	85.5	677	90.5
Pays all cost for all prescriptions	14	4.7	50	8.7	7	2.8	58	8.6
Pays all cost for some Prescriptions	17	5.8	36	6.3	13	5.2	45	6.6
Pays part of cost of prescriptions	262	88.8	477	83.2	225	90.7	565	83.5
Don't know	2	0.7	10	1.7	3	1.2	9	1.3
Insurance does not pay any cost for prescriptions	35	10.4	50	7.8	35	12.1	56	7.5
† 1489 includes 86 SA=Other which are not displayed due to small numbers. PD = purchase decision; SA = self assessment.								

Table 27shows the prevalence of reasons why participants chose SA=Yes despite reporting heart disease or heart problems.

Table 27. Reasons "Why you thought MEVACOR™ Daily was Appropriate for You to Use Even Though You Have Heart Problems/Disease?"

Provided Response†	LDL Paradigm(N=32)‡	Total C Paradigm(N=25)‡	Total(N=57)
Want to lower my cholesterol	7	9	16
Concerned with risk of heart attack	3	8	11
Previously taken this type of medication	7	3	10
Planning to talk to doctor	4	2	6
Less expensive than prescription medication	3	2	5
Doctor told me to take cholesterol medication	2	2	4
Family history	3	0	3
Cholesterol is high	2	1	3
Had condition in past/not currently	1	2	3
Do not have condition	1	2	3
No reason provided	2	1	3
Want to keep my cholesterol low/good	2	0	2
Condition is minor or controlled	0	2	2
Misunderstood information in label	2	0	2
Desire to lower cholesterol outweighs characteristic	2	0	2
Want to live longer	1	1	2
Meets other criteria	1	1	2
Total in right range	0	1	1
Did not notice information on label	1	0	1
Other Specify	5	4	9

† Participants could have provided up to 3 reasons for appropriateness.
‡ Number of participants who provided a response to the question are included. Protocol violators are excluded.

MO Comment: *The most common reasons were to lower my cholesterol, concerned with risk of heart attack, and previously taken this type of medication. The reasons were similar in the two study arms. Many of these reasons, like "planning to talk to doctor", qualified a subject to be mitigated.*

Table 28. Why you thought MEVACOR™ Daily was Appropriate for You to Use Even Though You Have Had a Stroke?"

Provided Response†	LDL Paradigm(N=10)‡	Total C Paradigm(N=6)‡	Total(N=16)
Concerned with risk of heart attack	2	1	3
Condition is minor or controlled	1	2	3
Had condition in past/not currently	1	2	3
Want to lower my cholesterol	2	0	2
Previously taken this type of medication	1	1	2
Family history	0	1	1
Cholesterol is high	0	1	1
Want to improve health	1	0	1
Doctor told me cholesterol is bad	1	0	1
Do not have condition	1	0	1
Did not notice information on label	1	0	1
Desire to lower cholesterol outweighs characteristic	1	0	1
Doctor told me to take cholesterol medication	1	0	1
Other Specify	0	1	1

† Participants could have provided up to 3 reasons for appropriateness.
Number of participants who provided a response to the question are included. Protocol violators are excluded.

MO Comment: *Common reasons given were that the condition is minor, controlled, or in the past. The stroke sample was small.*

Table 29. Why you thought MEVACOR™ Daily was Appropriate for You to Use Even Though You Have Diabetes?"

Provided Response†	LDL Paradigm(N=25)‡	Total C Paradigm(N=20)‡	Total(N=45)
Condition is minor or controlled	5	6	11
Want to lower my cholesterol	3	6	9
Planning to talk to the doctor	5	1	6
Did not notice information on label	4	2	6
Do not have condition	1	3	4
Cholesterol is high	1	2	3
Concerned with risk of heart attack	1	2	3
Previously taken this type of medication	1	1	2
I know my numbers are bad/high	2	0	2
Misunderstood information on label	1	1	2
Desire to lower cholesterol outweighs characteristic	2	0	2
Less expensive than prescription medication	1	0	1
Family history	0	1	1
Want to improve health	1	0	1
Doctor told me cholesterol is bad	0	1	1
Doctor told me to take cholesterol medication	1	0	1
Other Specify	2	1	3

† Participants could have provided up to 3 reasons for appropriateness.
‡ Number of participants who provided a response to the question are included. Protocol violators are excluded.

MO Comment: *The most common reason among diabetic subjects was "condition is minor or controlled". Six of 45 diabetics said they "did not notice information on label".*

Hierarchies

The Sponsor noted that some of the ineligibilities are of more clinical significance than others. The Sponsor proposed hierarchies of eligibility criteria, with all the specific criteria classified and ranked according to clinical importance. The Sponsor then determined how many subjects chose correctly according to reduced sets of eligibility criteria, by waiving the less important ineligibilities according to various hierarchies.

The Sponsor hierarchies included the following:

1. Safety Hierarchy - Focuses on key safety criteria in the following order: pregnant/breast-feeding, may become pregnant, allergy to lovastatin, interacting medications, lipid lowering medications, and liver problems.
2. Benefit Hierarchy - Focuses on key benefit criteria and includes age, lipid values (LDL-C or Total-C), and risk factors.
3. Combination Safety and Benefit Hierarchy - Combines the safety hierarchy with the key benefit criteria and includes: pregnant/breast-feeding, may become pregnant, allergy to lovastatin, interacting medications, lipid lowering medications, liver problems, age, risk factors, and lipid values (LDL-C or Total-C).
4. Benefit without Lipids Hierarchy - Includes age and risk factors. The rationale for excluding lipid values from this hierarchy is that there was evidence in the open-ended responses that many participants who did not know their numbers had an idea that they were in a moderate risk range. This was supported by the end of visit cholesterol test that demonstrated that many of these participants did have LDL-C or Total-C values within the range indicated for MEVACOR™ Daily. Further, the simvastatin Heart Protection Study (HPS), a mega-trial demonstrated that CHD risk is reduced similarly across the treatment group regardless of baseline lipid values. Thus, according to the Sponsor, there is evidence that if someone is within the age range and has a risk factor they could benefit from treatment with lovastatin, regardless of baseline cholesterol levels.
5. Expanded Benefit Hierarchy - Includes age, risk factors, heart disease, stroke, and diabetes

For the Sponsor Tables reproduced here, the column 'Correct vs. Specific Label Criteria' is a tabulation of the participants who responded that MEVACOR™ Daily was appropriate for them or that they wished to purchase MEVACOR™ Daily. The 'Talk to Doctor' column displays the number of participants that indicated that they would talk to their doctor either before they used the product or before they bought the product. The column labeled 'Mitigated Ineligibility Only for Criteria' indicates the number of participants who provided an open-ended response during the course of the interview that indicated that they may have had an understandable or acceptable reason for stating that they were appropriate for MEVACOR™ Daily despite this ineligibility. The column 'Total-Correct Plus Talk to Doctor and Mitigated' is a summation of the three previously discussed columns. Tables pertaining to SA have an additional section, 'Evidence of Not Understanding SA Question.' This indicates that a participant's response to an open-ended question provided clear evidence that they were either not thinking of the question in terms of "right now" or that they were thinking of the question in theoretical terms. A common example of this is a participant who responded "yes" to the SA question and "no" to the PD question and when asked why they did not wish to buy the product, may have stated that they did not want to buy because they did not meet a specific eligibility criterion. Obviously, this participant understood the label, knew they were ineligible, and did not want to use the product. There was a series of questions in the eCRF to understand a participant's potential misunderstanding of the SA question. The Sponsor states that many times the investigator misused or misunderstood this question and responded "yes" that the participant did not understand the SA question. The Sponsor also states that in several instances it was determined that there was not clear evidence of misunderstanding. Therefore, just because an investigator indicated that a participant did not understand the SA question does not mean that the participant is tabulated in that column in the tables that follow. For this series of tables, participants who displayed clear evidence of not understanding the SA question were taken out of the denominator to calculate the percent in the column "Total-Corrected plus Talk to the Doctor and Mitigated" from the column 'SA=Yes Revised Total.'

MO Comment: *A few examples of the Sponsor's hierarchy schemes are presented here. It should be noted that there may be differences in opinion on what should be mitigated between the Agency and Sponsor. It is may be difficult to mitigate accurately without knowing the complete medical history.*

Table 30 summarizes SA vs. Eligibility based on the safety hierarchy for the LDL-C paradigm. Safety criteria as defined in this hierarchy include pregnant or breast-feeding, may become pregnant, allergy to lovastatin, taking interacting medications, taking lipid lowering medications, and liver disease or problems. For the participants who responded SA=Yes, 81.3% met the safety criteria defined above, and that improves to approximately 91.4% if mitigating factors are included.

Table 30. Safety Hierarchy, LDL-C Arm

	SA=Yes (N=214)†								SA=Yes N=214 minus Participants with 'Evidence of Not Understanding SA Question'		
	Correct vs. Specific Label Criteria		'Talk to Doctor'		Mitigated Ineligibility Only for Criteria		Total-Corrected plus Talk to Doctor and Mitigated		'Evidence of Not Understanding SA Question'	SA=Yes Revised Total	Total-Corrected plus Talk to Doctor and Mitigated
Label Criteria	n	%	n	%	n	%	n	%	n	n	%
Pregnant/Breast-Feeding	214	100	0	0.0	0	0.0	214	100	0	214	100
May Become Pregnant	213	99.5	0	0.0	0	0.0	213	99.5	1	213	100
Allergy	213	99.5	0	0.0	0	0.0	213	99.5	1	213	100
Interacting Medications	210	98.1	3	1.4	0	0.0	213	99.5	1	213	100
Lipid Lowering Medications	174	81.3	17	7.9	0	0.0	191	89.3	5	209	91.4
Liver Problem	174	81.3	17	7.9	0	0.0	191	89.3	5	209	91.4

† Participants with missing data, participants whose eligibility could not be determined due to a data collection issue, and protocol violators are excluded.
LDL-C = low-density lipoprotein cholesterol; SA = self assessment.

MO Comment: *The safety hierarchy does not take into account clinically important eligibility criteria. This hierarchy, of those proposed by the Sponsor, gives the highest proportions of correct SA responses. Of note, there were few subjects in the LDL-C arm who had the conditions pertinent to the top four criteria. According to Sponsor Table 11-17 (Appendix), there were only 2 pregnant, 12 who may become pregnant, 4 with allergy, and 12 with interacting medications in the LDL arm.*

A second example of the results of defining hierarchies is shown in Table 31, with the percent correct SA in the LDL-C arm increasing from 21% to 56.8% with all mitigations per the Sponsor.

Table 31. Combination Safety and Benefit Hierarchy, LDL-C Arm

	SA=YES (N=214)†								SA=YES N=214 minus Participants with 'Evidence of Not Understanding SA Question'		
	Correct vs. Specific Label Criteria		'Talk to Doctor'		Mitigated Ineligibility Only for Criteria		Total-Corrected plus Talk to Doctor and Mitigated		'Evidence of Not Understanding SA Question'	SA=YES Revised Total	Total-Corrected plus Talk to Doctor and Mitigated
Label Criteria	N	%	N	%	N	%	N	%	N	N	%
Pregnant\breast-feeding	214	100	0	0.0	0	0.0	214	100	0	214	100
May become pregnant	213	99.5	0	0.0	0	0.0	213	99.5	1	213	100
Allergy	213	99.5	0	0.0	0	0.0	213	99.5	1	213	100
Interacting medications	210	98.1	3	1.4	0	0.0	213	99.5	1	213	100
Lipid lowering medications	174	81.3	17	7.9	0	0.0	191	89.3	5	209	91.4
Liver problem	174	81.3	17	7.9	0	0.0	191	89.3	5	209	91.4
Age	145	67.8	26	12.1	5	2.3	176	82.2	9	205	85.9
Risk factors	111	51.9	30	14.0	9	4.2	150	70.1	13	201	74.6
LDL cholesterol	45	21.0	43	20.1	25	11.7	113	52.8	15	199	56.8

† Excludes participants with missing data, participants with a procedural error, and protocol violators.
SA = self assessment.

MO Comment: *This hierarchy combines most of the clinically important eligibility criteria, except for CHD, stroke and diabetes.*

A third example of the results of defining hierarchies is shown in Table 32, with the percent correct SA in the LDL-C arm increasing from 40.7% to 70.5% with all mitigations per the Sponsor.

Table 32. Expanded Benefit Hierarchy, LDL-C Arm

	SA=Yes (N=214)†								SA=Yes N=214 minus Participants with 'Evidence of Not Understanding SA Question'		
	Correct vs. Specific Label Criteria		'Talk to Doctor'		Mitigated Ineligibility Only for Criteria		Total-Corrected plus Talk to Doctor and Mitigated		'Evidence of Not Understanding SA Question'	SA=Yes Revised Total	Total-Corrected plus Talk to Doctor and Mitigated
Label Criteria	n	%	n	%	n	%	n	%	n	n	%
Age	176	82.2	10	4.7	6	2.8	192	89.7	6	208	92.3
Risk Factors	140	65.4	15	7.0	10	4.7	165	77.1	10	204	80.9
Heart Disease	112	52.3	29	13.6	13	6.1	154	72.0	12	202	76.2
Stroke	111	51.9	29	13.6	13	6.1	153	71.5	12	202	75.7
Diabetes	101	47.2	34	15.9	15	7.0	150	70.1	13	201	74.6
Lipid Lowering Medications	87	40.7	40	18.7	14	6.5	141	65.9	14	200	70.5

† Participants with missing data, participants whose eligibility could not be determined due to a data collection issue, and protocol violators are excluded.
LDL-C = low-density lipoprotein cholesterol; SA = self assessment.

MO Comment: *This hierarchy combines several of the most clinically important eligibility criteria, but it does not include pregnancy/breastfeeding and lipid values.*

The FDA requested two additional hierarchies to be calculated. These were:

1. For SA=YES, the following criteria were applied in the order shown
   - Participants meet the age criteria (women ≥ 55 and men ≥ 45)
   - Participants are not on lipid lowering drugs
   - LDL-C values are within the 130-170 range (LDL paradigm)
   - Are not taking interacting medications
   - Risk factors

2. Also for SA=Yes, similarly apply the following criteria:
   - Participants meet the age criteria (women ≥ 55 and men ≥ 45)
   - Participants are not on lipid lowering drugs
   - LDL-C values are within the 130-170 range
   - Are not taking interacting medications
   - Do not have heart disease, stroke, or diabetes
   - Risk factors

The results for the LDL-C arm are shown in Table 33 and Table 34.

Table 33. FDA Hierarchy 1, LDL-C Arm

	SA=Yes (N=214)†								SA=Yes N=214 minus Participants with 'Evidence of Not Understanding SA Question'		
	Correct vs. Specific Label Criteria		'Talk to Doctor'		Mitigated Ineligibility Only for Criteria		Total-Correct plus Talk to Doctor and Mitigated		'Evidence of Not Understanding SA Question'	SA=Yes Revised Total	Total-Correct plus Talk to Doctor and Mitigated
Label Criteria	n	%	n	%	n	%	n	%	n	n	%
Age	176	82.2	10	4.7	6	2.8	192	89.7	6	208	92.3
Lipid-Lowering Medications	145	67.8	26	12.1	5	2.3	176	82.2	9	205	85.9
LDL Cholesterol	59	27.6	41	19.2	27	12.6	127	59.3	13	201	63.2
Interacting Medications	59	27.6	41	19.2	27	12.6	127	59.3	13	201	63.2
Risk Factors	45	21.0	43	20.1	25	11.7	113	52.8	15	199	56.8

† Participants with missing data, participants whose eligibility could not be determined due to a data collection issue and protocol violators are excluded.

Table 34. FDA Hierarchy 2, LDL-C Arm

	SA=Yes (N=214)†								SA=Yes N=214 minus Participants with 'Evidence of Not Understanding SA Question'		
	Correct vs. Specific Label Criteria		'Talk to Doctor'		Mitigated Ineligibility Only for Criteria		Total-Correct plus Talk to Doctor and Mitigated		'Evidence of Not Understanding SA Question'	SA=Yes Revised Total	Total-Correct plus Talk to Doctor and Mitigated
Label Criteria	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**n**	**%**
Age	176	82.2	10	4.7	6	2.8	192	89.7	6	208	92.3
Lipid-Lowering Medications	145	67.8	26	12.1	5	2.3	176	82.2	9	205	85.9
LDL Cholesterol	59	27.6	41	19.2	27	12.6	127	59.3	13	201	63.2
Interacting Medications	59	27.6	41	19.2	27	12.6	127	59.3	13	201	63.2
Heart Disease	56	26.2	42	19.6	28	13.1	126	58.9	13	201	62.7
Stroke	56	26.2	42	19.6	28	13.1	126	58.9	13	201	62.7
Diabetes	52	24.3	44	20.6	27	12.6	123	57.5	14	200	61.5
Risk Factors	38	17.8	46	21.5	25	11.7	109	50.9	16	198	55.1

† Participants with missing data, participants whose eligibility could not be determined due to a data collection issue and protocol violators are excluded.

The FDA hierarchy results for the Total-C arm (where the total-C criterion replaced the LDL-C criterion) are shown in Table 35 and Table 36.

Table 35. FDA Hierarchy 1, Total-C Arm

	SA=Yes (N=242)†								SA=Yes N=242 minus Participants with 'Evidence of Not Understanding SA Question'		
	Correct vs. Specific Label Criteria		'Talk to Doctor'		Mitigated Ineligibility Only for Criteria		Total-Correct plus Talk to Doctor and Mitigated		'Evidence of Not Understanding SA Question'	SA=Yes Revised Total	Total-Correct plus Talk to Doctor and Mitigated
Label Criteria	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**n**	**%**
Age	206	85.1	8	3.3	11	4.5	225	93.0	5	237	94.9
Lipid-Lowering Medications	174	71.9	21	8.7	10	4.1	205	84.7	7	235	87.2
Total Cholesterol	90	37.2	27	11.2	29	12.0	146	60.3	11	231	63.2
Interacting Medications	90	37.2	27	11.2	29	12.0	146	60.3	11	231	63.2
Risk Factors	85	35.1	27	11.2	29	12.0	141	58.3	11	231	61.0

† Participants with missing data, participants whose eligibility could not be determined due to a data collection issue and protocol violators are excluded.

Table 36. FDA Hierarchy 2, Total-C Arm

	SA=Yes (N=242)†								SA=Yes N=242 minus Participants with 'Evidence of Not Understanding SA Question'		
	Correct vs. Specific Label Criteria		'Talk to Doctor'		Mitigated Ineligibility Only for Criteria		Total-Correct plus Talk to Doctor and Mitigated		'Evidence of Not Understanding SA Question'	SA=Yes Revised Total	Total-Correct plus Talk to Doctor and Mitigated
Label Criteria	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**n**	**%**
Age	206	85.1	8	3.3	11	4.5	225	93.0	5	237	94.9
Lipid-Lowering Medications	174	71.9	21	8.7	10	4.1	205	84.7	7	235	87.2
Total Cholesterol	90	37.2	27	11.2	29	12.0	146	60.3	11	231	63.2
Interacting Medications	90	37.2	27	11.2	29	12.0	146	60.3	11	231	63.2
Heart Disease	85	35.1	28	11.6	31	12.8	144	59.5	11	231	62.3
Stroke	85	35.1	28	11.6	31	12.8	144	59.5	11	231	62.3
Diabetes	80	33.1	29	12.0	34	14.0	143	59.1	11	231	61.9
Risk Factors	76	31.4	29	12.0	33	13.6	138	57.0	11	231	59.7

† Participants with missing data, participants whose eligibility could not be determined due to a data collection issue and protocol violators are excluded.

MO Comment: *The FDA hierarchies were intended to list two versions of the most clinically important eligibility criteria, according to whether patients with heart disease, diabetes, or stroke should or should not be treated with OTC statins. There was not a consensus on the review team as to whether treatment of high risk patients is desirable from a public health perspective, because on the one hand those who are not under any treatment would benefit even from an OTC statin, but on the other hand they would not be adequately treated according to the current standard of care.*

The results in terms of percent totally correct, percent correct after mitigation, and percent correct after mitigations and exclusions for not understanding SA, were within the ranges found for the Sponsor hierarchies, and were similar to the results shown in Table 31 *for the Sponsor's Combined Safety and Benefit Hierarchy. The percent correct for FDA Hierarchy 1, in the LDL arm, is 21%. The percent correct after mitigations in the hierarchy increased to 52.8%. For Hierarchy 2, LDL arm, the percent correct is 17.8% with the percent correct increasing to 50.9% after mitigations.*

MO Comment: *None of the hierarchies (either from the Sponsor or from the FDA) was pre-specified, in advance of implementing the study. This procedural deficiency reduces the value of the hierarchies.*

Table 37. Summary of SA = Yes Decisions

Criterion	LDL Label (n=214)	Total-C Label (n=242)
Age	82%	85%
Lipid values	36%	50%
Additional risk factor	82%	75%
HDL	Not applicable	55%
All correct	26%	37%

MO Comment: *The Sponsor included* Table 37*, which summarizes the correct SA= Yes decisions for certain eligibility criteria, in the background package. In the LDL arm, 82% of subjects who said SA = Yes met the age criterion. Correctness of lipid values is based on the self-reported values, and in the LDL arm 36% of those who said SA = Yes met the lipid criterion (LDL value). A significantly higher proportion, 50% ($p<0.005$), of subjects in the Total-C arm who said SA = Yes met the lipid criterion (Total-C). Some subjects who were correct on any one of the criteria were incorrect on one or more of the others. The "all correct" row pertains to just the criteria listed in* Table 37*. The rates of correct self-selection considering all label criteria are 16% for SA in the LDL arm (*Figure 2*) and 27% for SA in the Total-C arm (*Figure 4*).*

6.1.5 Efficacy Conclusions

The SELECT study evaluated self-selection and purchase decisions in a population of 1520 consumers, comparing two label designs. One label required consumers to know their LDL-C and the other required knowledge of Total-C. The Agency has stated that the treatment paradigm for OTC lovastatin must be consistent with the ATP III treatment guidelines which use LDL-C

as a basis for treatment decisions. **The label for LDL-C paradigm is more consistent with ATP III than the Total-C label**.

Recruitment advertisements for SELECT stated that it was "important to know your four cholesterol numbers: total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides …to participate in the study ." Subjects were also informed that they would be asked to decide whether the product is appropriate for them to use. This advertising may have recruited a more informed population with subjects who were more likely to know their cholesterol profiles and may have been primed to pay extra attention to information on the label. These actions may have improved the correct self-selection rate.

The rates of correct self-selection (SA) and purchase decision (PD) responses were similar for the two label paradigms. **About 20% of subjects were completely correct in their SA or PD = Yes responses for either of the two arms**. The Sponsor analyzed the interview results to identify subjects who gave incorrect responses to SA and/or PD according to the label but whose open-ended responses nevertheless provided a rationale for their using the product; these ineligible subjects were said to be mitigated. The Sponsor found that almost half the ineligible subjects who incorrectly selected SA=Yes could be mitigated, raising the correct and mitigated proportion of subjects to about 50%.

The rationale given most often for mitigation was that the subject expressed an intention to speak to a doctor. Although subjects were not explicitly asked whether they wanted to talk to a doctor, they were given several opportunities to do so. The DNCE review team found it difficult to assess the subjects' original intentions after reading the label but prior to the interactions with the interviewer. The subject could have been brought to the realization that they should ask a doctor by the interview questioning. Nevertheless, this reviewer gave the benefit of the doubt, in that "talk to a doctor" was accepted for mitigation if mentioned in any of the opportunities. However, the reviewer did not agree with mitigation in cases where the subject was at high risk and should be treated with prescription medications, if the patient had previously taken prescription medication but had stopped because of a side effect, or if they had been prescribed a more potent statin and wanted to replace it with lovastatin.

An additional issue is that **even if the subject expresses an intention to talk to a doctor, the SELECT study has no means to evaluate whether the subject would actually do so if able to purchase the product OTC**. In addition, The SELECT study did not evaluate some issues pertinent to effective consumer use of OTC statins for primary prevention of CV events. Namely, consumers must understand that continued monitoring of serum lipid profiles is required and that the drug therapy must in most cases be continued for life. Moreover, treatment goals may need to be modified as new health conditions arise. There is only one line in a lengthy Drug Facts label that states "If you stop taking this product your cholesterol will go back up". SELECT also did not evaluate how consistently consumers will get follow up cholesterol testing to see if they are reaching their treatment goal. These issues were assessed in the CUSTOM actual use study in the previous submission of NDA 21-213, however the labels differed in their handling of these issues.

The Sponsor constructed several hierarchies of label eligibility criteria, whereby certain criteria they judged to be less clinically important could be waived. Several hierarchies were proposed, whereby the percent correct before mitigation ranged from about 21% to 80% depending on the hierarchy scheme. Then the proportion of correct plus mitigated subjects could be raised to about 90% in the best case and to about 50% in the worst case.

The FDA review team constructed two additional hierarchies for each label paradigm, based upon a subset of the label criteria which were judged to be the most clinically important. The **percent correct for FDA Hierarchy 1, in the LDL arm, is 21%. The percent correct after mitigations in the hierarchy increased to 52.8%.** For Hierarchy 2, LDL arm, the percent correct is 17.8% with the percent correct increasing to 50.9% after mitigations.

None of the hierarchies, either from the Sponsor or from the FDA, was defined a priori.

The **proportions of subjects who selected SA=Yes without knowing required cholesterol numbers was similar in the two arms**, although in the total SA populations there were **significantly more subjects who did not know their LDL-C** than those who did not know their total C. In the LDL-C arm, 268/714 (37.5%) did not know their LDL-C, but of these only 60/268 (22.4%) selected SA=Yes. In the Total-C arm, 149/708 (21%) did not know their Total-C, but of these 26/149 (17.4%) selected SA=Yes.

Many of the subjects who had LDL outside the eligible range nevertheless selected SA=Yes in the LDL-C arm. In the LDL-C arm, 52/122 (43%) of subjects who had LDL-C too high (above 170) still said SA = Yes, while 26/153(17%) of subject whose LDL-C was too low (below 130) also selected SA = Yes. Similarly, in the Total-C arm, 17/122 (14%) had total-C too low but selected SA = Yes, while also 79/223 (35%) had total-C too high but selected SA = Yes. In both arms, some of the subjects had LDL-C or total-C too low because they were already on prescription medications.

The Sponsor determined the Framingham coronary heart disease (CHD) risk for subjects who selected SA=Yes. About one third of subjects (men and women combined) who said SA=Yes in the LDL-C arm, and about 43% in the Total-C arm, had Framingham CHD risk of 5% to 20%, which is the range that the SELECT label intends to target for use of the product. Men who selected SA=Yes tended to have higher CHD risk than the women. About 40-55% of the men with SA=Yes fell in the 5% to 20% CHD risk range compared with approximately 25% of the women falling in this range. About 11% of men with SA=Yes had <5% CHD risk, but **over 40% of the women with SA=Yes had <5% CHD risk**. At such low values of CHD risk, it is not clear whether the benefit of using an OTC statin outweighs the risks of side effects.

The SELECT study evaluated the rates at which subjects with specific ineligibilities for who said SA=Yes. For instance, in the LDL-C arm, a population of concern is subjects with a heart problem or heart disease; here **33 subjects out of 68 with heart disease, or almost half, said the product was appropriate to use** (SA=Yes). Subjects at high CHD risk should be treated aggressively by prescription medications under the care of a physician. In addition, these high risk subjects should be under a physician's care for their primary condition, or for co morbid conditions, or they may need a combination of lipid-lowering therapies.

As shown in the Appendix Table A4 (Response to FDA Question), there were 220 women too young in the LDL-Arm SA population of 391 women (56.3%), and that 29 out of the 220 women (13.2%) who were too young responded SA=Yes. There were 101 women who responded SA=Yes, so of the women who responded SA=Yes, 29/101 (28.7%) were too young. Women who are below the age cutoff most often have Framingham risk below 5% and should decide not to take an OTC statin, especially if they may become pregnant.

The Sponsor investigated the reasons why subjects chose SA=Yes or PD=Yes incorrectly. The most frequent reasons for choosing SA=Yes, when the subject was already taking lipid-lowering medication, were to replace the prescription medication or specifically to replace it because of lower cost. The Sponsor also examined the reasons why subjects were interested in exploring non-prescription medicine rather than prescription medicine for cholesterol. The most frequent reasons cited by those with SA=Yes were less expensive (50%), convenience (29%), don't have to see the doctor (15%), and feels safer/less side effects (11.3%).

Also of concern is the prevalence for those **already on medication to lower blood lipid, cholesterol, or triglycerides, again as shown for SA=Yes: 44 subjects out of 140 subjects on these medications (31.4%) said the product was appropriate to use**. As these subjects were previously given prescription medication, it may not be appropriate for them to switch to an OTC statin without consulting a doctor, as they may not achieve their LDL goal.

Of the participants in SELECT who evaluated for SA (both study arms combined), 261/1492 (17.5%) were taking lipid-lowering medication. Similarly, of the participants who evaluated for PD, 259/1491 (17.4%) were taking lipid-lowering medication. From the results in Table 11 and Table 12 for the two study arms combined, 86 (33.0%) of the participants taking lipid-lowering medication stated that they were appropriate to use the product, and 58 (22.4%) decided that they would like to purchase the product.

Participants who had decided PD=Yes but who reported that they were already taking a lipid-lowering medication were asked if they planned to take the OTC Mevacor along with the prescription medicine or in place of it. About **half responded that they would replace their prescription medication, but about 30% said they would take Mevacor along with it.** Of the latter subjects, about one quarter said they would talk to a doctor.

On average, about 30% of participants with heart disease, stroke, or diabetes wanted to purchase the product. About two thirds of these subjects were not taking any lipid-lowering medications.

There were only **four participants in the total study population stated that they were pregnant and one participant who was breastfeeding. All of these individuals made acceptable decisions**. Twenty-two females stated that they may become pregnant. Of these participants, none of them decided to purchase the product. However, two participants stated that they were appropriate for the product. The sponsor mitigated both subjects on the basis of their open-ended responses. This reviewer disagrees with one of these mitigations, and the other is debatable. **It is difficult to extrapolate these results to women who may become pregnant, because of the small sample sizes** of pregnant women and women who say they may become pregnant. The procedure of

asking a women if she “thinks she may become pregnant” may underestimate the potential for use by pregnant women, since many pregnancies are unintended.

Also not specifically related to ATP III guidelines, there are other issues regarding whether consumers will use OTC statins effectively for primary prevention of CV events. Namely, they must understand that continued monitoring of serum lipid profiles is required and that the drug therapy must in most cases be continued for life. Moreover, treatment goals may need to be modified as new health conditions arise. There is only one line in a lengthy Drug Facts label that states “If you stop taking this product your cholesterol will go back up”. It is also not clear how consumers will get follow up cholesterol testing to see if they are reaching their treatment goal. These issues were assessed in the CUSTOM actual use study in the previous submission of NDA 21-213, however the labels differed in their handling of these issues.

10 APPENDICES

These supplementary tables are presented in numerical order according to the Sponsor's numbering. The following two tables are results of analyses requested by the FDA which do not correspond to tables in the SELECT study report, because of 1) separately analyzing men and women, and 2) a stricter application of the age criteria.

Table A4. Response to FDA Question, 9/24/07: Prevalence of Ineligibilities, Women only (LDL-C)

LDL-C Paradigm	Prevalence (SA)[†]	SA=Yes[†]	Prevalence (PD)[†]	PD=Yes[†]
Ineligibility Criteria	N (%) (% of evaluators with criteria)	N (%) (% SA=Yes)	N (%) (% of evaluators with criteria)	N (%) (% PD=Yes)
Too young[‡]	220/391 (56.3)	29/101 (28.7)	220/391 (56.3)	33/96 (34.4)
Pregnant or breast-feeding[‖]	2/391 (0.5)	0/101 (0.0)	2/391 (0.5)	0/96 (0.0)
May become pregnant[‖]	12/391 (3.1)	1/101 (1.0)	12/391 (3.1)	0/96 (0.0)
Heart problem/disease	30/391 (7.7)	12/101 (11.9)	30/391 (7.7)	11/96 (11.5)
Stroke	14/391 (3.6)	4/101 (4.0)	14/391 (3.6)	4/96 (4.2)
Diabetes	38/391 (9.7)	11/101 (10.9)	38/391 (9.7)	8/96 (8.3)
Liver disease/liver problem	14/391 (3.6)	1/101 (1.0)	14/391 (3.6)	1/96 (1.0)
Allergic to the ingredient	1/390 (0.3)	0/100 (0.0)	1/390 (0.3)	0/95 (0.0)
Medication to lower blood lipid, cholesterol or triglycerides	55/390 (14.1)	13/100 (13.0)	55/390 (14.1)	10/95 (10.5)
Taking other listed prescription medicines	4/390 (1.0)	0/100 (0.0)	4/390 (1.0)	0/95 (0.0)
Don't know HDL-C number[§‖]	157/371 (42.3)	30/93 (32.3)	157/386 (40.7)	28/94 (29.8)
HDL-C is too high[§‖]	88/371 (23.7)	25/93 (26.9)	93/386 (24.1)	29/94 (30.9)
Don't know LDL-C number[§]	156/370 (42.2)	28/93 (30.1)	156/385 (40.5)	27/94 (28.7)
LDL-C is too low[§]	70/370 (18.9)	6/93 (6.5)	77/385 (20.0)	7/94 (7.4)
LDL-C is too high[§]	63/370 (17.0)	29/93 (31.2)	66/385 (17.1)	32/94 (34.0)
Drink large quantities of grapefruit juice	1/388 (0.3)	0/100 (0.0)	1/388 (0.3)	0/96 (0.0)
Used cholesterol numbers from non-fasted test	7/129 (5.4)	0/40 (0.0)	7/129 (5.4)	0/32 (0.0)
Don't have any of the listed risk factors	113/391 (28.9)	23/101 (22.8)	113/391 (28.9)	24/96 (25.0)

[†] Protocol Violators are excluded.
[‡] The age criterion used in this assessment is women ≥55 years of age. This is not the same as the criterion specified in the protocol and Data Summarization Plan.
[§] Participants who were identified as having a procedural error which related to obtaining a cholesterol test and their SA or PD decisions were not included in respective decision categories.
[‖] Eligibility questions were only asked to female participants.

Table A6. Response to FDA Question, 9/24/07:Prevalence of Ineligibilities, Women (only) Total-C

Total-C Paradigm	Prevalence (SA) †	SA=Yes†	Prevalence (PD) †	PD=Yes†
Ineligibility Criteria	N§ (%) (% of evaluators with criteria)	N (%) (% SA=Yes)	N (%) (% of evaluators with criteria)	N (%) (% PD=Yes)
Too young‡	195/383 (50.9)	22/106 (20.8)	195/384 (50.8)	22/92 (23.9)
Pregnant or breast-feeding#	3/383 (0.8)	1/106 (0.9)	3/384 (0.8)	0/92 (0.0)
May become pregnant#	10/383 (2.6)	1/106 (0.9)	10/384 (2.6)	0/92 (0.0)
Heart problem/disease	22/383 (5.7)	9/106 (8.5)	22/384 (5.7)	8/92 (8.7)
Stroke	15/383 (3.9)	3/106 (2.8)	15/384 (3.9)	3/92 (3.3)
Diabetes	28/383 (7.3)	6/106 (5.7)	28/384 (7.3)	5/92 (5.4)
Liver disease/liver problem	7/383 (1.8)	1/106 (0.9)	7/384 (1.8)	1/92 (1.1)
Allergic to the ingredient	5/383 (1.3)	0/106 (0.0)	5/384 (1.3)	0/92 (0.0)
Medication to lower blood lipid, cholesterol or triglycerides	56/383 (14.6)	18/106 (17.0)	56/384 (14.6)	11/92 (12.0)
Taking other listed prescription medicines	7/383 (1.8)	1/106 (0.9)	7/384 (1.8)	1/92 (1.1)
Don't know HDL-C number¶#	147/367 (40.1)	24/98 (24.5)	148/377 (39.3)	22/91 (24.2)
HDL-C is too high¶#	80/367 (21.8)	21/98 (21.4)	81/377 (21.5)	21/91 (23.1)
Don't know Total-C number¶	90/368 (24.5)	11/98 (11.2)	90/378 (23.8)	10/91 (11.0)
Total-C is too low¶	55/368 (14.9)	5/98 (5.1)	57/378 (15.1)	4/91 (4.4)
Total-C is too high¶	128/368 (34.8)	40/98 (40.8)	134/378 (35.4)	46/91 (50.5)
Drink large quantities of grapefruit juice	0/382 (0.0)	0/105 (0.0)	0/383 (0.0)	0/91 (0.0)
Used cholesterol numbers from non-fasted test	6/142‖ (4.2)	2/49 (4.1)	6/143‖ (4.2)	2/32 (6.3)
Don't have any of the listed risk factors#	130/383 (33.9)	27/106 (25.5)	130/384 (33.9)	22/92 (23.9)

† Protocol Violators are excluded.
‡ The age criterion used in this assessment is women ≥55 years of age. This is not the same as the criterion specified in the protocol and Data Summarization Plan.
§ Excludes 1 Participant(s) with missing Self-Assessment
‖ Fasting Data is missing for 1 participant(s).
¶ Participants who were identified as having a procedural error which related to obtaining a cholesterol test and their SA or PD decisions were not included in respective decision categories.
# Eligibility questions were only asked to female participants.

The last table in this subsection is an analysis requested by the FDA to search for subjects who may have participated in more than one of the OTC Mevacor studies. The studies searched were the actual use study CUSTOM, the present study SELECT, the pre-SELECT label comprehension study, the pivotal label comprehension study, and the muscle comprehension study. Comparisons were made on the basis of the participants' initials, gender, city and year of birth, except that for CUSTOM and SELECT, the full date of birth was available. There were 31 SELECT subjects who may have also participated in CUSTOM.

Table A7. Numbers of Potential Duplicates between Studies

	#086 SELECT	Pre-SELECT Label Comp	#087 Pivotal Label Comp	#088 Muscle Comp
#084 CUSTOM	31	3	3	2
#086 SELECT		8	0	2
Pre-SELECT Label Comp			10	3
#087 Pivotal Label Comp				2

10.1 Supplementary Sponsor Tables from SELECT

Sponsor Table 10-1 Number of Participants by Study Site – Two Study Arms Combined

			Self-Assessment (N=1499)†			Purchase Decision (N=1499)‡	
	Calls (N=5107)‖	Appointment Kept (N=1528)§, ‖	SA=Yes (N=494)	SA=No (N=916)	SA=Other (N=87)	PD=Yes (N=431)	PD=No (N=1065)
Site Name	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Skytop, OH	60 (1.2%)	60 (3.9%)	22 (4.5%)	34 (3.7%)	2 (2.3%)	15 (3.5%)	43 (4.0%)
Delhi, OH	80 (1.6%)	80 (5.2%)	18 (3.6%)	59 (6.4%)	3 (3.4%)	14 (3.2%)	66 (6.2%)
Westheimer (Houston), TX	222 (4.3%)	222 (14.5%)	76 (15.4%)	143 (15.6%)	2 (2.3%)	66 (15.3%)	155 (14.6%)
Jones Plaza (Houston), TX	102 (2.0%)	102 (6.7%)	17 (3.4%)	77 (8.4%)	7 (8.0%)	21 (4.9%)	80 (7.5%)
Dallas, TX	139 (2.7%)	138 (9.0%)	55 (11.1%)	76 (8.3%)	7 (8.0%)	41 (9.5%)	97 (9.1%)
Fort Worth, TX	108 (2.1%)	108 (7.1%)	44 (8.9%)	54 (5.9%)	7 (8.0%)	42 (9.7%)	64 (6.0%)
Sun City, AZ	99 (1.9%)	99 (6.5%)	31 (6.3%)	55 (6.0%)	11 (12.6%)	18 (4.2%)	79 (7.4%)
Tempe, AZ	49 (1.0%)	49 (3.2%)	14 (2.8%)	34 (3.7%)	0 (0.0%)	13 (3.0%)	35 (3.3%)
Aurora, CO	106 (2.1%)	106 (6.9%)	33 (6.7%)	62 (6.8%)	9 (10.3%)	29 (6.7%)	75 (7.0%)
Denver North, CO	101 (2.0%)	101 (6.6%)	40 (8.1%)	55 (6.0%)	4 (4.6%)	41 (9.5%)	58 (5.4%)
Bridgeton, MO	99 (1.9%)	99 (6.5%)	38 (7.7%)	56 (6.1%)	3 (3.4%)	31 (7.2%)	66 (6.2%)
ST. Louis, MO	100 (2.0%)	100 (6.5%)	21 (4.3%)	64 (7.0%)	15 (17.2%)	17 (3.9%)	83 (7.8%)
Blaine, MN	116 (2.3%)	116 (7.6%)	37 (7.5%)	65 (7.1%)	10 (11.5%)	45 (10.4%)	67 (6.3%)
Bloomington, MN	139 (2.7%)	139 (9.1%)	48 (9.7%)	82 (9.0%)	7 (8.0%)	38 (8.8%)	97 (9.1%)

† Includes 2 participants with missing Self-Assessment.
‡ Includes 3 participants with missing Purchase Decision.
§ Excludes one participant who did not come to the site but whose disposition was inappropriately assigned - investigator error.
‖ Includes 9 participants who kept appointments but were not assigned a study site because they discontinued the study (Refused to continue with study procedures).
N=Number of participants for all sites combined.
n=Number of participants by site.
PD=Purchase Decision; SA=Self Assessment.

Sponsor Table 10-8 for LDL-C Arm, Demographic Characteristics

	Self Assessment(N=754)†			Purchase Decision(N=754)‡	
	SA=Yes (N=235)	SA=No (N=471)	SA=Other (N=47)	PD=Yes (N=203)	PD=No (N=548)
Gender					
Male	134 (57.0%)	209 (44.4%)	18 (38.3%)	107 (52.7%)	252 (46.0%)
Female	101 (43.0%)	262 (55.6%)	29 (61.7%)	96 (47.3%)	296 (54.0%)
Age (years)					
<40	9 (3.8%)	100 (21.2%)	6 (12.8%)	5 (2.5%)	110 (20.1%)
Male	4 (1.7%)	47 (10.0%)	2 (4.3%)	3 (1.5%)	50 (9.1%)
Female	5 (2.1%)	53 (11.3%)	4 (8.5%)	2 (1.0%)	60 (10.9%)
40 to 44	22 (9.4%)	46 (9.8%)	1 (2.1%)	21 (10.3%)	48 (8.8%)
Male	19 (8.1%)	23 (4.9%)	1 (2.1%)	18 (8.9%)	25 (4.6%)
Female	3 (1.3%)	23 (4.9%)	0 (0.0%)	3 (1.5%)	23 (4.2%)
45 to 49	35 (14.9%)	84 (17.8%)	4 (8.5%)	32 (15.8%)	91 (16.6%)
Male	28 (11.9%)	29 (6.2%)	3 (6.4%)	21 (10.3%)	39 (7.1%)
Female	7 (3.0%)	55 (11.7%)	1 (2.1%)	11 (5.4%)	52 (9.5%)
50 to 54	35 (14.9%)	87 (18.5%)	3 (6.4%)	34 (16.7%)	91 (16.6%)
Male	21 (8.9%)	33 (7.0%)	1 (2.1%)	17 (8.4%)	38 (6.9%)
Female	14 (6.0%)	54 (11.5%)	2 (4.3%)	17 (8.4%)	53 (9.7%)
55 to 59	42 (17.9%)	63 (13.4%)	6 (12.8%)	36 (17.7%)	76 (13.9%)
Male	20 (8.5%)	29 (6.2%)	2 (4.3%)	16 (7.9%)	36 (6.6%)
Female	22 (9.4%)	34 (7.2%)	4 (8.5%)	20 (9.9%)	40 (7.3%)
60 to 64	43 (18.3%)	34 (7.2%)	9 (19.1%)	36 (17.7%)	50 (9.1%)
Male	19 (8.1%)	16 (3.4%)	3 (6.4%)	14 (6.9%)	24 (4.4%)
Female	24 (10.2%)	18 (3.8%)	6 (12.8%)	22 (10.8%)	26 (4.7%)
65 to 69	23 (9.8%)	24 (5.1%)	11 (23.4%)	22 (10.8%)	35 (6.4%)
Male	13 (5.5%)	11 (2.3%)	4 (8.5%)	12 (5.9%)	15 (2.7%)
Female	10 (4.3%)	13 (2.8%)	7 (14.9%)	10 (4.9%)	20 (3.6%)
70 to 74	17 (7.2%)	18 (3.8%)	4 (8.5%)	13 (6.4%)	25 (4.6%)
Male	6 (2.6%)	12 (2.5%)	1 (2.1%)	5 (2.5%)	13 (2.4%)
Female	11 (4.7%)	6 (1.3%)	3 (6.4%)	8 (3.9%)	12 (2.2%)
>=75	9 (3.8%)	15 (3.2%)	3 (6.4%)	4 (2.0%)	22 (4.0%)
Male	4 (1.7%)	9 (1.9%)	1 (2.1%)	1 (0.5%)	12 (2.2%)
Female	5 (2.1%)	6 (1.3%)	2 (4.3%)	3 (1.5%)	10 (1.8%)

Sponsor Table 10-8 continued

	Self Assessment(N=754)[†]			Purchase Decision(N=754)[‡]	
	SA=Yes (N=235)	SA=No (N=471)	SA=Other (N=47)	PD=Yes (N=203)	PD=No (N=548)
Mean Age ± SD	56.4 ± 10.54	49.6 ± 12.82	57.9 ± 12.64	56.0 ± 9.68	50.7 ± 13.17
Male	54.6 ± 10.17	50.3 ± 13.59	56.1 ± 13.11	54.0 ± 9.73	51.1 ± 13.34
Female	58.7 ± 10.62	49.0 ± 12.16	59.1 ± 12.44	58.1 ± 9.22	50.4 ± 13.03
Median Age	56	50	61	56	51
Male	53	51	59	53	51
Female	59	50	61	59	51
Age Range	24 to 86	18 to 84	29 to 81	34 to 86	18 to 84
Male	34 to 86	20 to 84	29 to 81	34 to 86	20 to 84
Female	24 to 86	18 to 80	31 to 78	34 to 86	18 to 82
Racial Origin					
Asian	4 (1.7%)	7 (1.5%)	1 (2.1%)	1 (0.5%)	11 (2.0%)
Black	40 (17.0%)	127 (27.0%)	7 (14.9%)	29 (14.3%)	145 (26.5%)
Hispanic American	18 (7.7%)	36 (7.6%)	4 (8.5%)	20 (9.9%)	39 (7.1%)
Native American	1 (0.4%)	10 (2.1%)	0 (0.0%)	1 (0.5%)	10 (1.8%)
White	169 (71.9%)	276 (58.6%)	35 (74.5%)	150 (73.9%)	327 (59.7%)
Other	3 (1.3%)	15 (3.2%)	0 (0.0%)	2 (1.0%)	16 (2.9%)
Literacy (Determined by REALM SCORE)					
Low Literacy	28 (11.9%)	57 (12.1%)	10 (21.3%)	27 (13.3%)	68 (12.4%)
Non Low Literacy	207 (88.1%)	414 (87.9%)	37 (78.7%)	176 (86.7%)	480 (87.6%)

[†] Includes 1 Participant(s) with missing Self-Assessment.
[‡] Includes 3 Participant(s) with missing Purchase Decision.
PD = purchase decision; SA = self assessment.

Sponsor Table 10-9 for Total-C Arm, Demographic Characteristics

	Self Assessment (N=745)†			Purchase Decision (N=745)	
	SA=Yes (N=259)	SA=No (N=445)	SA=Other (N=40)	PD=Yes (N=228)	PD=No (N=517)
Gender					
Male	153 (59.1%)	189 (42.5%)	19 (47.5%)	136 (59.6%)	225 (43.5%)
Female	106 (40.9%)	256 (57.5%)	21 (52.5%)	92 (0.4%)	292 (56.5%)
Age (years)					
<40	10 (3.9%)	101 (22.7%)	3 (7.5%)	9 (3.9%)	105 (20.3%)
Male	6 (2.3%)	44 (9.9%)	2 (5.0%)	5 (2.2%)	47 (9.1%)
Female	4 (1.5%)	57 (12.8%)	1 (2.5%)	4 (1.8%)	58 (11.2%)
40 to 44	23 (8.9%)	56 (12.6%)	4 (10.0%)	22 (9.6%)	61 (11.8%)
Male	23 (8.9%)	26 (5.8%)	4 (10.0%)	21 (9.2%)	32 (6.2%)
Female	0 (0.0%)	30 (6.7%)	0 (0.0%)	1 (0.4%)	29 (5.6%)
45 to 49	29 (11.2%)	61 (13.7%)	5 (12.5%)	29 (12.7%)	66 (12.8%)
Male	24 (9.3%)	27 (6.1%)	2 (5.0%)	22 (9.6%)	31 (6.0%)
Female	5 (1.9%)	34 (7.6%)	3 (7.5%)	7 (3.1%)	35 (6.8%)
50 to 54	41 (15.8%)	75 (16.9%)	4 (10.0%)	33 (14.5%)	87 (16.8%)
Male	28 (10.8%)	30 (6.7%)	1 (2.5%)	23 (10.1%)	36 (7.0%)
Female	13 (5.0%)	45 (10.1%)	3 (7.5%)	10 (4.4%)	51 (9.9%)
55 to 59	56 (21.6%)	46 (10.3%)	8 (20.0%)	54 (23.7%)	56 (10.8%)
Male	30 (11.6%)	19 (4.3%)	3 (7.5%)	31 (13.6%)	21 (4.1%)
Female	26 (10.0%)	27 (6.1%)	5 (12.5%)	23 (10.1%)	35 (6.8%)
60 to 64	52 (20.1%)	51 (11.5%)	7 (17.5%)	43 (18.9%)	68 (13.2%)
Male	23 (8.9%)	22 (4.9%)	2 (5.0%)	20 (8.8%)	27 (5.2%)
Female	29 (11.2%)	29 (6.5%)	5 (12.5%)	23 (10.1%)	41 (7.9%)
65 to 69	27 (10.4%)	24 (5.4%)	3 (7.5%)	22 (9.6%)	32 (6.2%)
Male	11 (4.2%)	9 (2.0%)	2 (5.0%)	10 (4.4%)	12 (2.3%)
Female	16 (6.2%)	15 (3.4%)	1 (2.5%)	12 (5.3%)	20 (3.9%)
70 to 74	16 (6.2%)	17 (3.8%)	3 (7.5%)	10 (4.4%)	26 (5.0%)
Male	7 (2.7%)	5 (1.1%)	2 (5.0%)	3 (1.3%)	11 (2.1%)
Female	9 (3.5%)	12 (2.7%)	1 (2.5%)	7 (3.1%)	15 (2.9%)
>=75	5 (1.9%)	14 (3.1%)	3 (7.5%)	6 (2.6%)	16 (3.1%)
Male	1 (0.4%)	7 (1.6%)	1 (2.5%)	1 (0.4%)	8 (1.5%)
Female	4 (1.5%)	7 (1.6%)	2 (5.0%)	5 (2.2%)	8 (1.5%)

Sponsor Table 10-9 continued

	Self Assessment (N=745)†			Purchase Decision (N=745)	
	SA=Yes (N=259)	SA=No (N=445)	SA=Other (N=40)	PD=Yes (N=228)	PD=No (N=517)
Mean Age ± SD	56.2 ± 9.81	49.4 ± 13.61	56.6 ± 11.03	56.0 ± 9.44	50.5 ± 13.59
Male	53.8 ± 9.11	49.0 ± 13.56	54.5 ± 12.15	53.6 ± 8.75	49.9 ± 13.46
Female	59.6 ± 9.80	49.7 ± 13.66	58.5 ± 9.83	59.5 ± 9.37	50.9 ± 13.71
Median Age	56	50	56	56	51
Male	54	49	55	54	50
Female	60	50	58	60	52
Age Range	19 to 83	18 to 86	38 to 82	30 to 83	18 to 86
Male	34 to 78	18 to 82	38 to 75	34 to 78	18 to 82
Female	19 to 83	18 to 86	39 to 82	30 to 83	18 to 86
Racial Origin					
Asian	8 (3.1%)	11 (2.5%)	0 (0.0%)	6 (2.6%)	13 (2.5%)
Black	55 (21.2%)	132 (29.7%)	4 (10.0%)	46 (20.2%)	145 (28.0%)
Hispanic American	15 (5.8%)	37 (8.3%)	2 (5.0%)	16 (7.0%)	38 (7.4%)
Native American	3 (1.2%)	3 (0.7%)	0 (0.0%)	3 (1.3%)	3 (0.6%)
White	171 (66.0%)	254 (57.1%)	34 (85.0%)	153 (67.1%)	307 (59.4%)
Other	7 (2.7%)	8 (1.8%)	0 (0.0%)	4 (1.8%)	11 (2.1%)
Literacy (Determined by REALM SCORE)					
Low Literacy	32 (12.4%)	69 (15.5%)	3 (7.5%)	21 (9.2%)	83 (16.1%)
Non Low Literacy	227 (87.6%)	376 (84.5%)	37 (92.5%)	207 (90.8%)	434 (83.9%)

† Includes 1 participant with missing Self Assessment.
PD=Purchase Decision; SA=Self Assessment.

Sponsor Table 11-8 for LDL-C Arm: Label Eligibility versus PD

	Purchase Decision vs. Eligibility Per Label (N=732)†		
	Correct Purchase Decision 565(77.2%)		Incorrect Purchase Decision 167(22.8%)
	Eligible Per Label	Not Eligible Per Label	Not Eligible Per Label
Participant Purchase Decision	**n**	**n**	**n**
Yes	29		167
No	17	519	

† Excludes 3 participants with missing purchase decision and 19 participants with missing data, procedural errors related to timing of a requested cholesterol test, and protocol violators.

Sponsor Table 11-9 for Total-C Arm: Label Eligibility versus PD

	Purchase Decision vs. Eligibility Per Label (N=725)†		
	Correct Purchase Decision 557(76.8%)		Incorrect Purchase Decision 168(23.2%)
	Eligible Per Label	Not Eligible Per Label	Not Eligible Per Label
Participant Purchase Decision	**n**	**n**	**n**
Yes	55		168
No	26	476	

† Excludes 20 participants with missing data, procedural errors related to timing of a requested cholesterol test, and protocol violators.

Sponsor Table 11-17 LDL-C Arm Prevalence of Label Ineligibilities

LDL-C Paradigm Ineligibility Criteria	Prevalence (SA)† N‡ (%) (% of evaluators with criteria)	SA=Yes† N (%) (% SA=Yes)	Prevalence (PD)† N§ (%) (% of evaluators with criteria)	PD=Yes† N (%) (% PD=Yes)
Too young	290/752 (38.6)	41/235 (17.4)	290/750 (38.7)	44/203 (21.7)
Pregnant or breast-feeding¶	2/391 (0.5)	0/101 (0.0)	2/391 (0.5)	0/96 (0.0)
May become pregnant¶	12/391 (3.1)	1/101 (1.0)	12/391 (3.1)	0/96 (0.0)
Heart problem/disease	68/752 (9.0)	33/235 (14.0)	68/750 (9.1)	22/203 (10.8)
Stroke	26/752 (3.5)	9/235 (3.8)	26/750 (3.5)	7/203 (3.4)
Diabetes	79/752 (10.5)	25/235 (10.6)	79/750 (10.5)	15/203 (7.4)
Liver disease/liver problem	23/752 (3.1)	2/235 (0.9)	23/750 (3.1)	2/203 (1.0)
Allergic to the ingredient	4/750 (0.5)	0/234 (0.0)	4/748 (0.5)	0/202 (0.0)
Medication to lower blood lipid, cholesterol or triglycerides	140/750 (18.7)	44/234 (18.8)	138/748 (18.4)	27/202 (13.4)
Taking other listed prescription medicines	12/751 (1.6)	3/234 (1.3)	12/749 (1.6)	1/202 (0.5)
Don't know HDL-C number‖¶	157/371 (42.3)	30/93 (32.3)	157/386 (40.7)	28/94 (29.8)
HDL-C is too high‖¶	88/373 (23.6)	25/93 (26.9)	93/388 (24.0)	29/96 (30.2)
Don't know LDL-C number‖	268/714 (37.5)	60/217 (27.6)	271/738 (36.7)	52/199 (26.1)
LDL-C is too low‖	153/714 (21.4)	26/217 (12.0)	162/738 (22.0)	22/199 (11.1)
LDL-C is too high‖	122/714 (17.1)	52/217 (24.0)	127/738 (17.2)	56/199 (28.1)
Drink large quantities of grapefruit juice	1/747 (0.1)	0/233 (0.0)	1/745 (0.1)	0/201 (0.0)
Used cholesterol numbers from non-fasted test	17/285 (6.0)	0/101 (0.0)	17/283 (6.0)	2/81 (2.5)
Don't have any of the listed risk factors	202/752 (26.9)	45/235 (19.1)	201/750 (26.8)	40/203 (19.7)

† Protocol violators are excluded.
‡ Excludes 1 participant with missing SA.
§ Excludes 3 participants with missing PD.
‖ Participants who were identified as having a procedural error which related to obtaining a cholesterol test and their SA or PD decisions were not included in respective decision categories.
¶ Eligibility questions were only asked to female participants.
PD = purchase decision; SA = self assessment.

Sponsor Table 11-17 (LDL-C Paradigm) and Sponsor Table 11-18 (Total-C Paradigm) show the prevalence of specific label ineligibilities, from the second point of view (see Prevalence of Ineligibilities discussion above, Section 6.1.4 Efficacy Findings). These tables list the number of participants in the entire population who made an SA or PD decision with that label ineligibility and then list the number of people with positive decisions (SA=Yes or PD=Yes) who had that label ineligibility.

Sponsor Table 11-18 for Total-C Arm

Total-C Paradigm Ineligibility Criteria	Prevalence (SA)† N‡ (%) (% of evaluators with criteria)	SA=Yes† N (%) (% SA=Yes)	Prevalence (PD)† N (%) (% of evaluators with criteria)	PD=Yes† N (%) (% PD=Yes)
Too young	281/743 (37.8)	41/259 (15.8)	281/744 (37.8)	37/228 (16.2)
Pregnant or breast-feeding#	3/383 (0.8)	1/106 (0.9)	3/384 (0.8)	0/92 (0.0)
May become pregnant#	10/383 (2.6)	1/106 (0.9)	10/384 (2.6)	0/92 (0.0)
Heart problem/disease	51/743 (6.9)	23/259 (8.9)	51/744 (6.9)	19/228 (8.3)
Stroke	20/743 (2.7)	6/259 (2.3)	20/744 (2.7)	5/228 (2.2)
Diabetes	56/743 (7.5)	17/259 (6.6)	56/744 (7.5)	14/228 (6.1)
Liver disease/liver problem	16/743 (2.2)	1/259 (0.4)	16/744 (2.2)	1/228 (0.4)
Allergic to the ingredient	7/742 (0.9)	0/259 (0.0)	7/743 (0.9)	0/228 (0.0)
Medication to lower blood lipid, cholesterol or triglycerides	121/742 (16.3)	42/259 (16.2)	121/743 (16.3)	31/228 (13.6)
Taking other listed prescription medicines	9/742 (1.2)	1/259 (0.4)	9/743 (1.2)	2/228 (0.9)
Don't know HDL-C number¶#	147/367 (40.1)	24/98 (24.5)	148/377 (39.3)	22/91 (24.2)
HDL-C is too high¶#	80/367 (21.8)	21/98 (21.4)	81/377 (21.5)	21/91 (23.1)
Don't know Total-C number¶	149/708 (21.0)	26/245 (10.6)	149/732 (20.4)	21/225 (9.3)
Total-C is too low¶	122/708 (17.2)	17/245 (6.9)	130/732 (17.8)	14/225 (6.2)
Total-C is too high¶	223/708 (31.5)	79/245 (32.2)	232/732 (31.7)	88/225 (39.1)
Drink large quantities of grapefruit juice	0/738 (0.0)	0/256 (0.0)	0/739 (0.0)	0/226 (0.0)
Used cholesterol numbers from non-fasted test	12/303§ (4.0)	4/122‖ (3.3)	12/304§ (3.9)	4/105‖ (3.8)
Don't have any of the listed risk factors#	130/383 (33.9)	27/106 (25.5)	130/384 (33.9)	22/92 (23.9)

† Protocol violators are excluded.
‡ Excludes 1 participant with missing SA.
§ Fasting data is missing for 2 participants.
‖ Fasting data is missing for 1 participant.
¶ Participants who were identified as having a procedural error which related to obtaining a cholesterol test and their SA or PD decisions were not included in respective decision categories.
# Eligibility questions were only asked to female participants.
PD = purchase decision; SA = self assessment.

Sponsor Table 11-21, Women <54 years

	LDL-C Paradigm ‡	Total-C Paradigm ‡	Combined Paradigm ‡
Self Assessment: No. of Women who are too young	199	178	377
SA=Yes	26 (13.1%)	16 (9.0%)	42 (11.1%)
SA=No	166 (83.4%)	156 (87.6%)	322 (85.4%)
SA=Other	7 (3.5%)	6 (3.4%)	13 (3.4%)
Purchase Decision: No. of Women who are too young	205	182	387
PD=Yes	30 (14.6%)	18 (9.9%)	48 (12.4%)
PD=No	175 (85.4%)	164 (90.1%)	339 (87.6%)

† Women less than 54 years old as per Data Summarization Plan.
‡ Excludes participants with missing SA or PD decision, participants with missing data, participants with a procedural error and protocol violators.
PD = purchase decision; SA = self assessment.

10.2 Line-by-Line Labeling Review

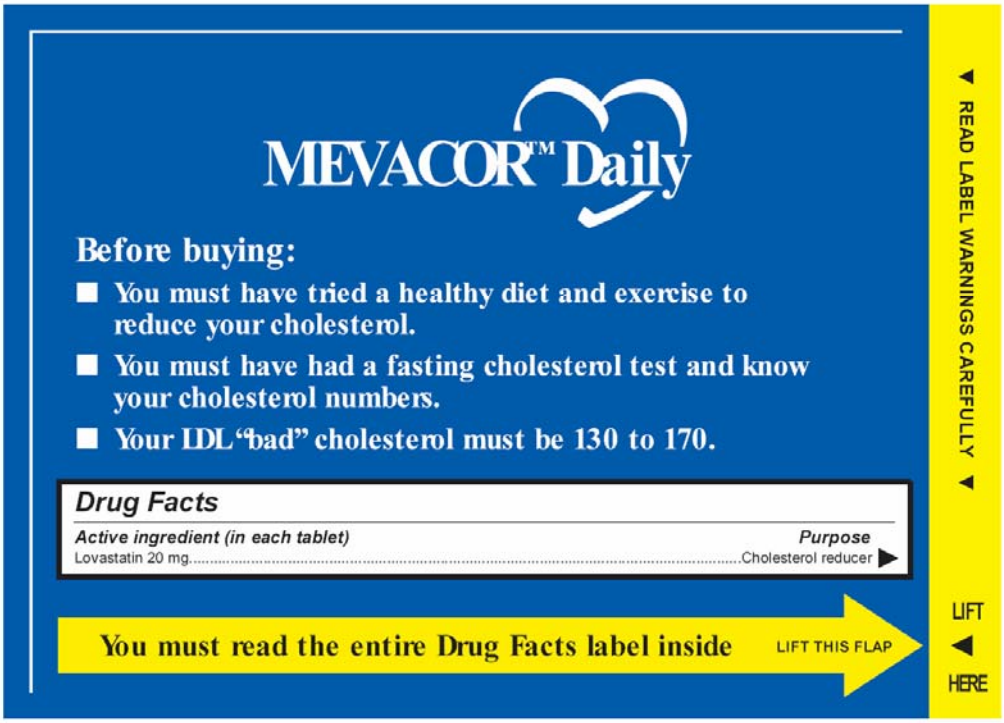
SELECT Label, LDL-C Paradigm

PROPOSED PACKAGE LABEL (LDL)

FRONT PANEL

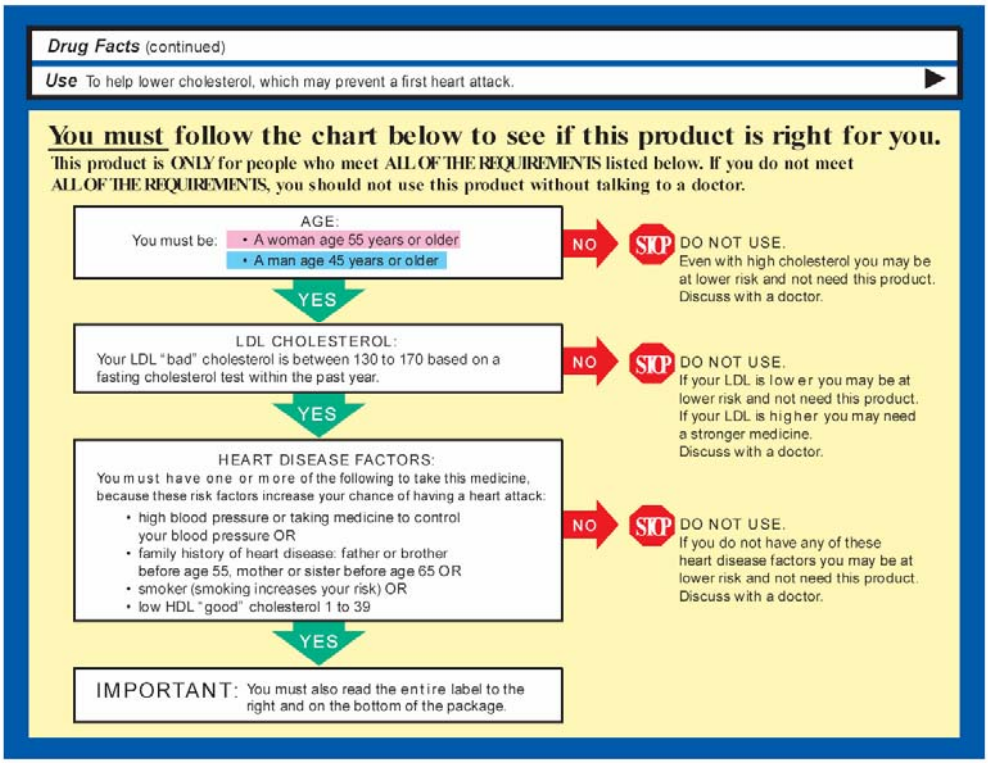
PROPOSED PACKAGE LABEL (LDL)

OUTSIDE PANEL



PROPOSED PACKAGE LABEL (LDL)

INSIDE FLAP – PANEL ON LEFT



PROPOSED PACKAGE LABEL (LDL)

INSIDE FLAP – PANEL ON RIGHT

Drug Facts (continued)

Warnings

Do not use if you know you are allergic to lovastatin

Ask a doctor before use if you

- are taking prescription cholesterol medicines. Do not substitute. This product is probably not strong enough for you
- have LDL "bad" cholesterol 171 to 400. You are at higher risk for heart disease
- are a woman under age 55 or a man under age 45. You may be at lower risk for heart disease
- are a woman with high HDL "good" cholesterol 60 to 200. You may be at lower risk for heart disease
- have liver disease
- have had heart disease
- have had a stroke
- have diabetes

Ask a doctor or pharmacist before use if you are

- unsure of your cholesterol numbers or have not had a fasting cholesterol test within the last year
- taking any of the following, as certain drugs or foods can cause interactions:
  - cholesterol medicines
  - oral antibiotics
  - oral antifungals
  - drugs for irregular heartbeat
  - HIV protease inhibitors
  - cyclosporine (immune suppressant)
  - nefazodone (antidepressant)
  - large quantities of grapefruit juice (more than 1 quart daily)

When using this product, talk to a doctor if there is a change in your health, such as a new prescription medicine or a new medical condition.

Stop use and ask a doctor if you develop any unexplained muscle pain, weakness or tenderness. This can be a sign of a rare but serious side effect.

If pregnant or breast-feeding, or think you may become pregnant, do not use. This product may cause problems in the unborn child.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- this product is only for you if
  - you are a woman 55 years or older or a man 45 years or older and
  - your LDL "bad" cholesterol is between 130 and 170 and
  - you also have one or more of the following heart disease factors which increase your chance of a heart attack:
    - high blood pressure or taking medicine to control your blood pressure or
    - family history of heart disease: father or brother before age 55, mother or sister before age 65 or
    - smoker (smoking increases your risk) or
    - low HDL "good" cholesterol 1 to 39

▼ READ LABEL WARNINGS CAREFULLY ▼

LIFT ◀ HERE

PROPOSED PACKAGE LABEL (LDL)

BOTTOM PANEL

Drug Facts (continued)

Directions (continued)

- take only one tablet daily with your evening meal (your body makes more cholesterol at night)
- continue to eat a healthy diet and exercise
- after 6 weeks get a fasting cholesterol test to see if your LDL "bad" cholesterol has reached a healthy level:
  - LDL "bad" cholesterol 1 to 129. It's working, keep taking it daily and test your cholesterol once a year
  - LDL "bad" cholesterol 130 to 400. This product may not be strong enough for you.
    Talk to a doctor about using a prescription cholesterol medicine
- if you stop taking this product, your cholesterol will go back up

Other information

- before using this product, you must have tried a healthy diet and exercise to reduce your cholesterol
- before using this product, read the materials enclosed in this package for additional important information
- store at 5°-30° C (41°- 86° F)

Inactive ingredients Butylated hydroxyanisole (BHA), cellulose, FD&C blue No. 2 aluminum lake, lactose, magnesium stearate, and starch

Questions? Call toll-free 1-800-_____ from __a.m. to __p.m. (ET) Monday to Friday or visit our website anytime at www.xxxxxxx.com

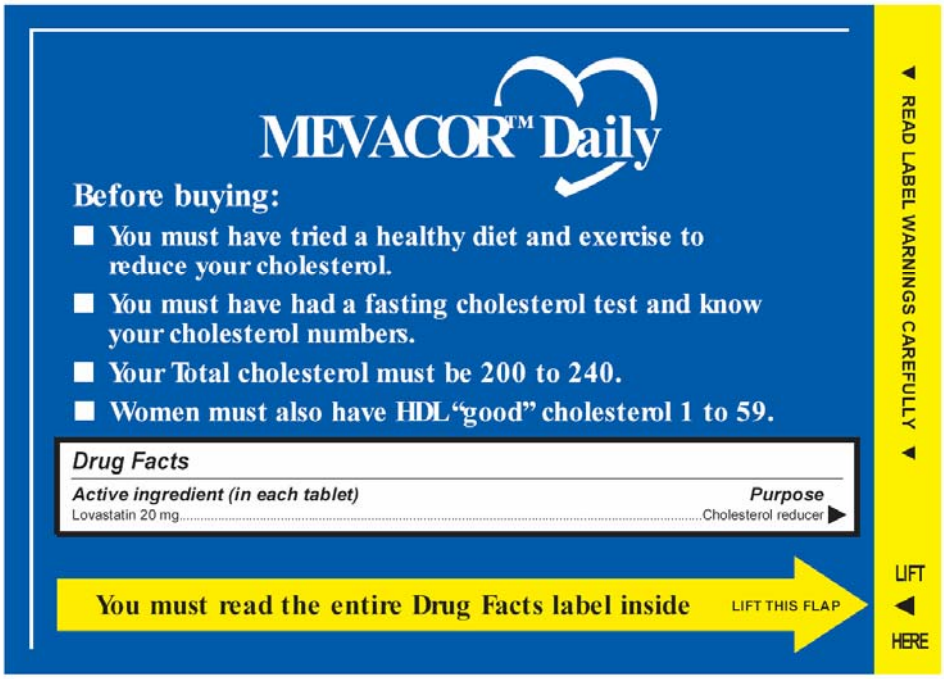
SELECT Label, Total Cholesterol Paradigm

SELECT Package Label (TOTAL)

FRONT PANEL

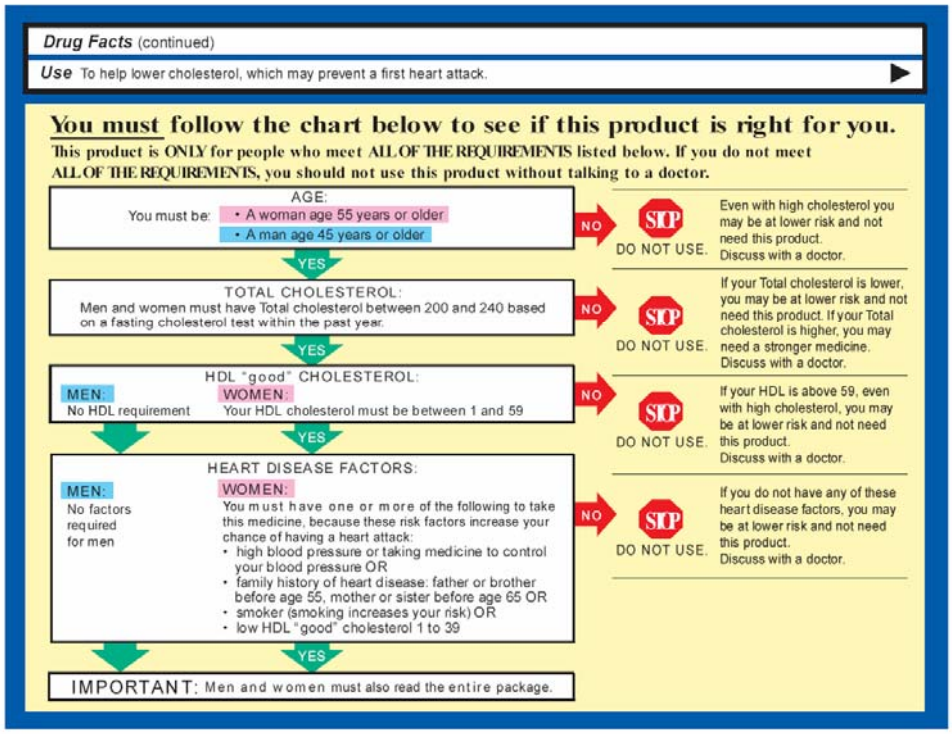
SELECT Package Label (TOTAL)

OUTSIDE PANEL



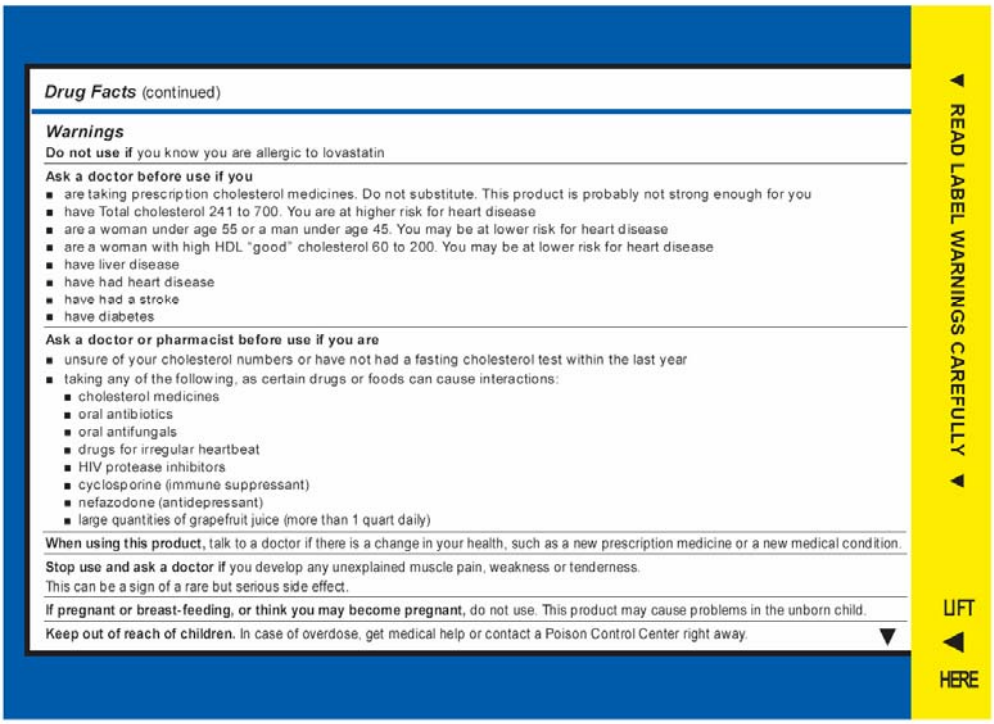
SELECT Package Label (TOTAL)

INSIDE FLAP – PANEL ON LEFT



SELECT Package Label (TOTAL)

INSIDE FLAP – PANEL ON RIGHT



Drug Facts (continued)

Warnings

Do not use if you know you are allergic to lovastatin

Ask a doctor before use if you

- are taking prescription cholesterol medicines. Do not substitute. This product is probably not strong enough for you
- have Total cholesterol 241 to 700. You are at higher risk for heart disease
- are a woman under age 55 or a man under age 45. You may be at lower risk for heart disease
- are a woman with high HDL "good" cholesterol 60 to 200. You may be at lower risk for heart disease
- have liver disease
- have had heart disease
- have had a stroke
- have diabetes

Ask a doctor or pharmacist before use if you are

- unsure of your cholesterol numbers or have not had a fasting cholesterol test within the last year
- taking any of the following, as certain drugs or foods can cause interactions:
  - cholesterol medicines
  - oral antibiotics
  - oral antifungals
  - drugs for irregular heartbeat
  - HIV protease inhibitors
  - cyclosporine (immune suppressant)
  - nefazodone (antidepressant)
  - large quantities of grapefruit juice (more than 1 quart daily)

When using this product, talk to a doctor if there is a change in your health, such as a new prescription medicine or a new medical condition.

Stop use and ask a doctor if you develop any unexplained muscle pain, weakness or tenderness.
This can be a sign of a rare but serious side effect.

If pregnant or breast-feeding, or think you may become pregnant, do not use. This product may cause problems in the unborn child.

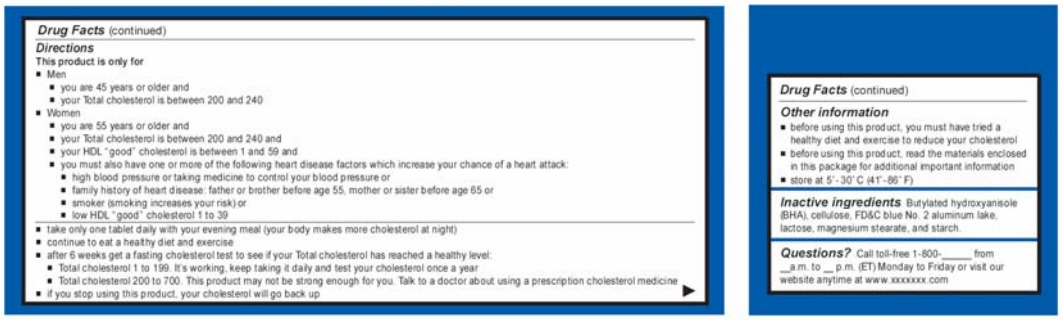
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

▼ READ LABEL WARNINGS CAREFULLY ▼

LIFT ◀ HERE

SELECT Package Label (TOTAL)

BOTTOM PANEL



Drug Facts (continued)

Directions

This product is only for

- Men
  - you are 45 years or older and
  - your Total cholesterol is between 200 and 240
- Women
  - you are 55 years or older and
  - your Total cholesterol is between 200 and 240 and
  - your HDL "good" cholesterol is between 1 and 59 and
  - you must also have one or more of the following heart disease factors which increase your chance of a heart attack:
    - high blood pressure or taking medicine to control your blood pressure or
    - family history of heart disease: father or brother before age 55, mother or sister before age 65 or
    - smoker (smoking increases your risk) or
    - low HDL "good" cholesterol 1 to 39

- take only one tablet daily with your evening meal (your body makes more cholesterol at night)
- continue to eat a healthy diet and exercise
- after 6 weeks get a fasting cholesterol test to see if your Total cholesterol has reached a healthy level:
  - Total cholesterol 1 to 199: It's working, keep taking it daily and test your cholesterol once a year
  - Total cholesterol 200 to 700: This product may not be strong enough for you. Talk to a doctor about using a prescription cholesterol medicine
- if you stop using this product, your cholesterol will go back up

▶

Drug Facts (continued)

Other information

- before using this product, you must have tried a healthy diet and exercise to reduce your cholesterol
- before using this product, read the materials enclosed in this package for additional important information
- store at 5°-30°C (41°-86°F)

Inactive ingredients Butylated hydroxyanisole (BHA), cellulose, FD&C blue No. 2 aluminum lake, lactose, magnesium stearate, and starch.

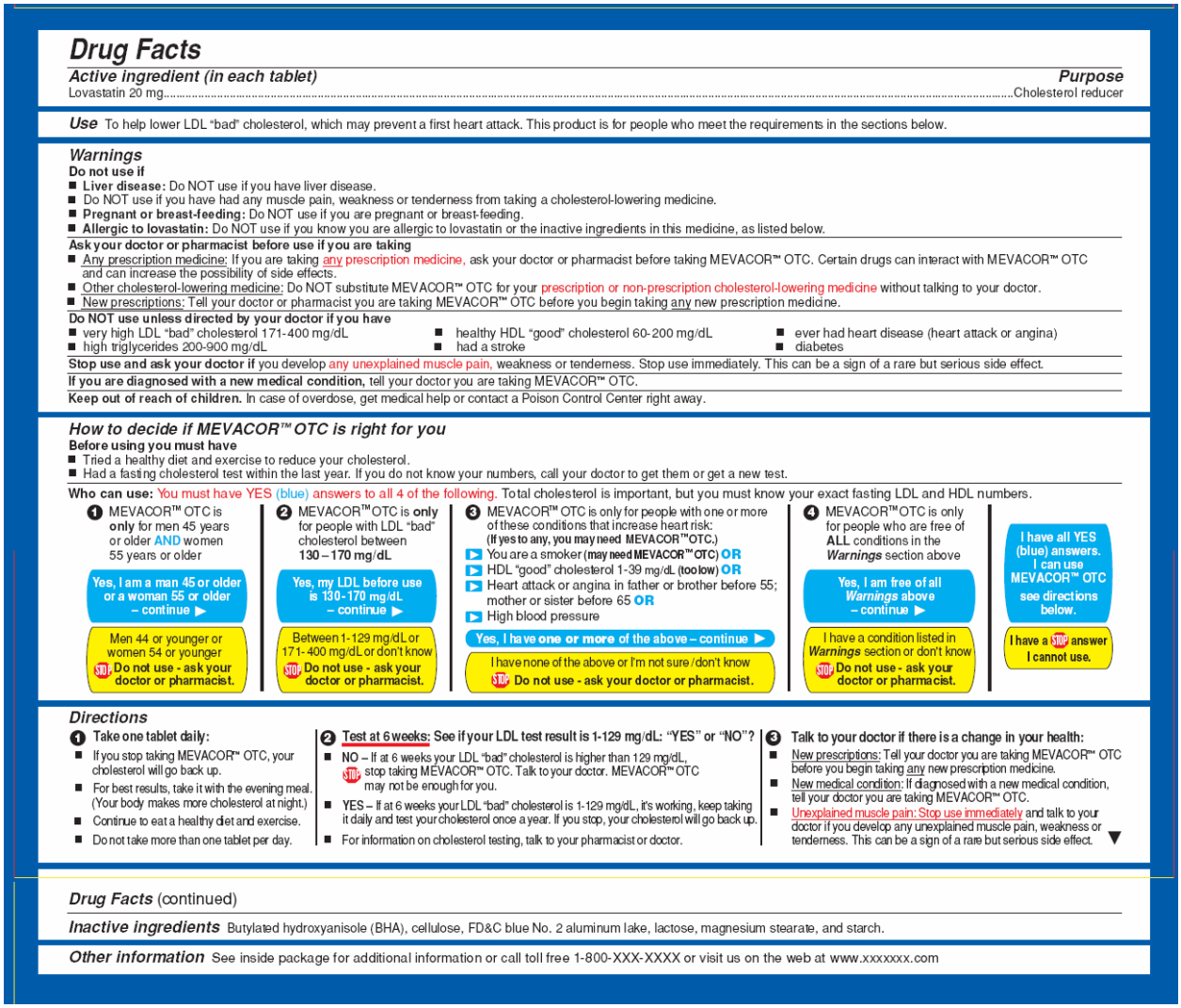
Questions? Call toll-free 1-800-_____ from __a.m. to __ p.m. (ET) Monday to Friday or visit our website anytime at www.xxxxxxx.com

CUSTOM Label

FRONT PANEL

CUSTOM Label

BACK PANEL



Drug Facts

Active ingredient (in each tablet) — **Purpose**
Lovastatin 20 mg ..... Cholesterol reducer

Use To help lower LDL "bad" cholesterol, which may prevent a first heart attack. This product is for people who meet the requirements in the sections below.

Warnings

Do not use if
- **Liver disease:** Do NOT use if you have liver disease.
- Do NOT use if you have had any muscle pain, weakness or tenderness from taking a cholesterol-lowering medicine.
- **Pregnant or breast-feeding:** Do NOT use if you are pregnant or breast-feeding.
- **Allergic to lovastatin:** Do NOT use if you know you are allergic to lovastatin or the inactive ingredients in this medicine, as listed below.

Ask your doctor or pharmacist before use if you are taking
- Any prescription medicine: If you are taking any prescription medicine, ask your doctor or pharmacist before taking MEVACOR™ OTC. Certain drugs can interact with MEVACOR™ OTC and can increase the possibility of side effects.
- Other cholesterol-lowering medicine: Do NOT substitute MEVACOR™ OTC for your prescription or non-prescription cholesterol-lowering medicine without talking to your doctor.
- New prescriptions: Tell your doctor or pharmacist you are taking MEVACOR™ OTC before you begin taking any new prescription medicine.

Do NOT use unless directed by your doctor if you have
- very high LDL "bad" cholesterol 171-400 mg/dL
- high triglycerides 200-900 mg/dL
- healthy HDL "good" cholesterol 60-200 mg/dL
- had a stroke
- ever had heart disease (heart attack or angina)
- diabetes

Stop use and ask your doctor if you develop any unexplained muscle pain, weakness or tenderness. Stop use immediately. This can be a sign of a rare but serious side effect.

If you are diagnosed with a new medical condition, tell your doctor you are taking MEVACOR™ OTC.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

How to decide if MEVACOR™ OTC is right for you

Before using you must have
- Tried a healthy diet and exercise to reduce your cholesterol.
- Had a fasting cholesterol test within the last year. If you do not know your numbers, call your doctor to get them or get a new test.

Who can use: You must have YES (blue) answers to all 4 of the following. Total cholesterol is important, but you must know your exact fasting LDL and HDL numbers.

1. MEVACOR™ OTC is **only** for men 45 years or older **AND** women 55 years or older
   - Yes, I am a man 45 or older or a woman 55 or older – continue ▶
   - Men 44 or younger or women 54 or younger — STOP Do not use - ask your doctor or pharmacist.
2. MEVACOR™ OTC is **only** for people with LDL "bad" cholesterol between **130 – 170 mg/dL**
   - Yes, my LDL before use is 130-170 mg/dL – continue ▶
   - Between 1-129 mg/dL or 171-400 mg/dL or don't know — STOP Do not use - ask your doctor or pharmacist.
3. MEVACOR™ OTC is only for people with one or more of these conditions that increase heart risk: **(If yes to any, you may need MEVACOR™ OTC.)**
   - ▶ You are a smoker **(may need MEVACOR™ OTC) OR**
   - ▶ HDL "good" cholesterol 1-39 mg/dL **(too low) OR**
   - ▶ Heart attack or angina in father or brother before 55; mother or sister before 65 **OR**
   - ▶ High blood pressure

   Yes, I have **one or more** of the above – continue ▶
   I have none of the above or I'm not sure / don't know — STOP Do not use - ask your doctor or pharmacist.
4. MEVACOR™ OTC is only for people who are free of **ALL** conditions in the ***Warnings*** section above
   - Yes, I am free of all ***Warnings*** above – continue ▶
   - I have a condition listed in ***Warnings*** section or don't know — STOP Do not use - ask your doctor or pharmacist.

I have all YES (blue) answers. I can use MEVACOR™ OTC see directions below.

I have a STOP answer I cannot use.

Directions

1. **Take one tablet daily:**
   - If you stop taking MEVACOR™ OTC, your cholesterol will go back up.
   - For best results, take it with the evening meal. (Your body makes more cholesterol at night.)
   - Continue to eat a healthy diet and exercise.
   - Do not take more than one tablet per day.
2. **Test at 6 weeks: See if your LDL test result is 1-129 mg/dL: "YES" or "NO"?**
   - NO – If at 6 weeks your LDL "bad" cholesterol is higher than 129 mg/dL, STOP stop taking MEVACOR™ OTC. Talk to your doctor. MEVACOR™ OTC may not be enough for you.
   - YES – If at 6 weeks your LDL "bad" cholesterol is 1-129 mg/dL, it's working, keep taking it daily and test your cholesterol once a year. If you stop, your cholesterol will go back up.
   - For information on cholesterol testing, talk to your pharmacist or doctor.
3. **Talk to your doctor if there is a change in your health:**
   - New prescriptions: Tell your doctor you are taking MEVACOR™ OTC before you begin taking any new prescription medicine.
   - New medical condition: If diagnosed with a new medical condition, tell your doctor you are taking MEVACOR™ OTC.
   - Unexplained muscle pain: Stop use immediately and talk to your doctor if you develop any unexplained muscle pain, weakness or tenderness. This can be a sign of a rare but serious side effect. ▼

Drug Facts (continued)

Inactive ingredients Butylated hydroxyanisole (BHA), cellulose, FD&C blue No. 2 aluminum lake, lactose, magnesium stearate, and starch.

Other information See inside package for additional information or call toll free 1-800-XXX-XXXX or visit us on the web at www.xxxxxxx.com

REFERENCES

1. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP)Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001; 285(19):2486-2497.
2. Grundy SM et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation*. 2004; 110:227-239.

FDA Briefing Document

NDA 21-213

Mevacor™ Daily (lovastatin) Tablets, 20 mg

Merck & Co., Inc.

Advisory Committee – December 13, 2007

Clinical Review of Safety and Efficacy
Division of Metabolism and Endocrinology Products

Mevacor™ Daily Briefing Document

Nonprescription Drugs and
Endocrine and Metabolic Drugs Advisory Committees Meeting

December 13, 2007

NDA 21-213

Sponsor: Merck and Company

Medical Reviewer: Eileen M. Craig, M.D.

Medical Team Leader and Deputy Division Director: Eric G. Colman, M.D.

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This review is not final; additional information from the Advisory Committee and other review disciplines will be considered prior to finalization of the review and recommendations for regulatory action.

If used as directed by the LDL-C label paradigm, lovastatin 20 mg is a reasonably safe and effective drug for the treatment of hyperlipidemia in the nonprescription setting. However, the self-selection and actual use studies, SELECT and CUSTOM, have not convinced this reviewer that there is adequate consumer comprehension of the proposed product label to ensure safe and effective use of this product.

1.2 Recommendation on Postmarketing Actions

None at this time

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Merck is seeking to market MEVACOR™ Daily 20 mg tablet to reduce cholesterol for men (45 years of age and over) and women (55 years of age and over) with low density lipoprotein cholesterol (LDL-C) between 130 and 170 mg/dL, who also have one or more additional risk factors for coronary heart disease. This subset of individuals falls into a primary prevention of CHD population with less than a 20% 10-year CHD risk.

This is Merck's third attempt to switch Mevacor from prescription to non-prescription status. The original NDA 21-213 sought to switch lovastatin 10 mg from Rx to over-the-counter (OTC) status and was submitted on December 10, 1999. The data were presented at the Advisory Committee on July 13, 2000. The NDA was found to be nonapprovable, based on the data reviewed. Several deficiencies were raised by the Agency in the October 6, 2000 not approvable (NA) letter:

1. Neither the rationale for treating the proposed target population with Mevacor 10 mg in the OTC setting, nor a favorable benefit/risk ratio for such treatment has been adequately established.
2. The data did not demonstrate that consumers can understand and adequately implement treatment to a defined goal or that there is an identifiable population of consumers for

whom treatment with a fixed dose of Mevacor, without titration to reach a treatment goal, would represent an acceptable standard of care.

3. Consumers' ability to self-select and adequately comply/adhere with chronic therapy, as well as recognize the risks of therapy, was not demonstrated.
4. The sponsor did not provide adequate justification for deleting the recommendation for hepatic transaminase monitoring for Mevacor 10 mg when used in the OTC setting.
5. The data did not adequately demonstrate the ability of consumers to comprehend the risks associated with concomitant use of Mevacor with numerous interacting drugs.
6. The sponsor has not adequately addressed the risks to the fetus of potential Mevacor use by women who are pregnant or of childbearing potential in the OTC setting.

The second submission on August 24, 2004 was Merck's complete response to the October 6, 2000 NA letter. The data were presented at the Advisory Committee on January 13 and 14, 2005. The NDA was found to be nonapprovable, based on the data reviewed. Several deficiencies were raised by the Agency in the February 23, 2005 not approvable (NA) letter:

1. Failure of the clinical program to demonstrate adequate consumer comprehension of the proposed product label that will ensure the safe and effective use of the product. Consumers did not correctly self-select use of the product based on labeled criteria. Only half of the subjects who purchased and used Mevacor OTC selected correctly. In the Custom Study, only 75% of subjects who developed muscle pain made a correct decision about use of Mevacor OTC.
2. It has been established that knowledge of cholesterol values at baseline and during treatment with a lipid-lowering drug is necessary to establish the appropriateness and adequacy of therapy. This clinical development program failed to demonstrate that consumers will or can utilize cholesterol values correctly in the selection and deselection of Mevacor 20 mg.
3. The Mevacor OTC program reveals a majority of consumers requiring the assistance of a healthcare provider to select and de-select therapy. This finding would suggest that hypercholesterolemia is not an appropriate medical condition for nonprescription drug therapy.
4. Adequate data on the hepatic risk of lovastatin in patients with asymptomatic liver disease was not provided in the resubmission for Mevacor OTC to address the safe use of this product in the nonprescription setting. To address this deficiency, the applicant must provide sufficient evidence that the risk of hepatotoxicity is minimal in patients with common asymptomatic liver diseases in order to support removal of the current recommendation to monitor hepatic transaminases or provide sufficient evidence that consumers can make clinical safety assessments of hepatic risks before initiating therapy with nonprescription lovastatin.
5. The proposed label for nonprescription lovastatin was inadequate in discouraging the purchase and use of this product by women of childbearing potential who are at minimal risk for cardiovascular disease, but who are at risk for inadvertent exposure during pregnancy. To address this deficiency, the applicant must modify the nonprescription label and test consumer comprehension and consumer self-selection to ensure adequate consumer understanding of the risks of drug exposure during pregnancy.

In support of this current resubmission, requesting to switch Mevacor™ 20 mg from prescription to non-prescription status, the applicant has provided results of two label comprehension studies, The Muscle Warning Comprehension Study (P088) and The Pivotal Label Comprehension study (P087), a non-drug, self-selection study entitled "Self Evaluation of Lovastatin to Enhance Cholesterol Treatment (SELECT, P086) and proposed OTC labeling. No new clinical data were provided. Safety was assessed with an integrated summary of safety, published literature and a retrospective cohort database study entitled "Study of potential hepatotoxicity of lovastatin in the Northern California Kaiser Permanente liver disease population".

1.3.2 Efficacy

The efficacy of lovastatin as a lipid-lowering agent was established in several placebo-controlled efficacy trials during its development as a prescription drug. To support the efficacy of the 20 mg dose in the targeted OTC population, the applicant reanalyzed the data from the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) which was reviewed at the 2005 Advisory Committee meeting. The extrapolation of clinical benefit with this dose to the proposed population was problematic, as the analysis of AFCAPS/TexCAPS was a non-randomized comparison of treatment groups and the AFCAPS cohort did not accurately reflect the OTC population, as the former could be titrated up to a 40 mg dose to attain a lower LDL-C target of therapy (<110 mg/dL), and the risk reductions achieved in AFCAPS/TexCAPS reflected lovastatin 20 to 40 mg use in a 5-year clinical trial where compliance and modifications of other risk factors for heart disease were likely better than in an OTC population. However, this analysis did provide the best assessment of the benefits of Mevacor 20 mg for nonprescription use. While a true number needed to treat (NNT) or relative risk reduction could not be assigned to this patient population and treatment approach, it was reasonable to expect an overall benefit provided issues of compliance, monitoring, and other risk factor modifications were adequately addressed. However, the extent of population benefit and of individual risk reduction with lesser degrees of compliance and shorter terms of treatment is not known. The Advisory Committee agreed with DMEP's assessment that the applicant had proposed a patient population that merits therapy with lovastatin 20 mg, and that this dose would effectively lower cholesterol levels to a degree that would represent a clinical benefit.

If Mevacor Daily is approved for non-prescription use, this reviewer recommends that, to the extent feasible, information be placed on the package labeling that describes an estimate of clinical benefit for the consumer.

This reviewer approached this submission using the LDL-C label paradigm. If the applicant proposes that the Total Cholesterol (TC) label paradigm should be the label for MEVACOR™ Daily, they must provide evidence that demonstrates that the eligibility criteria in that label (for both men and women) target the same CHD risk population as the LDL-C label. Also, they must provide evidence that consumers using the TC label can appropriately assess their treatment goal which, as per NCEP ATP III guidelines, is based on an LDL-C target.

It is important to note that for optimal efficacy and avoidance of under-treatment, the consumer must appropriately self-select based on LDL level and CVD risk factor profile and must be able to take appropriate action based on response (e.g., discontinue and seek physician intervention if

response is inadequate). Additionally, the consumer should understand that management of hypercholesterolemia is chronic. Adherence to medications and compliance to diet and life-style modifications are essential components of this management. Consumers must also understand that their individual risks for heart disease may change over time based on age, development of cardiovascular disease, or other factors (e.g., elevated blood pressure, development of diabetes). With these changes, consumers must understand that their therapeutic target may be lower and that they may have to seek appropriate management to achieve these new goals. Finally, the field of lipid biology, atherosclerosis, and cardiovascular risk management will evolve over time as new data emerge. A nonprescription program that will be affected by changing treatment guidelines must be adaptable to these and other changes in the state of the relevant basic and clinical science in order to ensure appropriate consumer behavior and ongoing safety and efficacy of the non-prescription treatment regimen.

1.3.3 Safety

Data from controlled clinical trials and post-marketing spontaneous adverse event reporting support the conclusion that muscle and hepatic toxicity are rare events that do not offset the benefits associated with long–term use of lovastatin 20 mg in otherwise healthy individuals. The hepatic risks of lovastatin 20 mg daily in patients with baseline liver disease of certain etiologies have been addressed in this application. The large data-base study found that exposure to lovastatin in patients with baseline liver disease was not associated with an increased risk of adverse hepatic outcomes. While no prospective investigations in patients with diverse forms of asymptomatic liver disease have been conducted with lovastatin, in this reviewer's opinion, the lack of hepatic enzyme testing in the non-prescription setting for this 20 mg lovastatin dose is not likely to pose a significant safety risk. Thus, the applicant has provided sufficient evidence that the risk of hepatotoxicity is minimal in patients with common asymptomatic liver diseases to address the safe use of this product in the nonprescription setting.

Other safety concerns include drug-drug interactions which affect the risk of myopathy and exposure during pregnancy. The applicant proposes to manage these risks through labeling.

Deficiencies in SELECT that impact on the safe and effective use of this product include:

- 13% (29/220) of the women in the LDL-C paradigm who were too young made a positive self-assessment decision
- 29% (29/101) of women with a positive self-assessment decision were too young
- ~11% of men and over 40% of women with a positive self-assessment decision were of low CHD risk (<5% risk of CHD in 10 years)
- 22% (60/268) of the participants who did not know their LDL-C value made a positive self-assessment decision in the LDL-C paradigm
- 43% (52/122) of participants with a self-reported LDL-C higher than 170 mg/dL made a positive self-assessment decision; 17% (26/153) of participants with a self-reported LDL-C lower than 130 mg/dL made a positive self-assessment decision
- On average, about 30% of participants with CHD, diabetes mellitus, or stroke wanted to purchase the product

- Over 30% of participants already taking a lipid-lowering medication made a positive self-assessment decision. Over 50% of those who made a positive purchase decision but were already on lipid-lowing medications stated they would take Mevacor Daily "in place of" their lipid-lowering medication and over 25% would take Mevacor Daily along with their lipid-lowering medication. The 3 most commonly taken lipid-lowering medications used by participants in the LDL-C paradigm were atorvastatin, simvastatin, and rosuvastatin—significantly more potent statins than lovastatin

Finally, the prescription-to-nonprescription switch of Mevacor 20 mg must not augment the risk of the drug in the prevention of cardiovascular disease. For optimally safe use, the consumer must appropriately self-select as eligible for therapy after excluding factors that would increase the risk of drug side effects (e.g., pregnancy, use of an interacting drug) and elect discontinuation of therapy when situations arise that would alter the risk of therapy (e.g., newly prescribed interacting drug, development of myopathy).

This reviewer believes that the question regarding nonprescription lovastatin 20 mg is less about the benefit and safety of the drug, which has been documented in large, randomized clinical trials. Rather, the key question and underlying implication of this submission is whether chronic, asymptomatic conditions such as hyperlipidemia, hypertension, diabetes mellitus and osteoporosis can be appropriately and safely treated by the consumer and if this approach best serves the individual and the public health.

If Mevacor Daily is approved, stronger labeling language regarding consumers already taking a lipid-lowering prescription medication as well as consumers with a history of diabetes, heart disease and stroke is warranted.

1.3.4 Dosing Regimen and Administration

The proposed nonprescription dose of lovastatin is 20 mg once daily with the evening meal.

1.3.5 Drug-Drug Interactions

No new information on drug-drug interactions was provided in this submission. As per the prescription label, the risk of myopathy/rhabdomyolysis is increased by concomitant use of lovastatin with the following:

- Potent inhibitors of CYP3A4: such as itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, or large quantities of grapefruit juice (>1 quart daily)
- Gemfibrozil
- Other fibrates or ≥1 g/day of niacin
- Cyclosporine or danazol
- Amiodarone or verapamil

1.3.6 Special Populations

A retrospective cohort study provided sufficient evidence that the risk of hepatotoxicity is minimal in patients with common asymptomatic liver diseases.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Mevacor™ (lovastatin), a cholesterol lowering agent isolated from a strain of Aspergillus Terreus, is a specific inhibitor of HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate. The conversion of HMG-CoA to mevalonate is an early and rate limiting step in the biosynthetic pathway for cholesterol. Mevacor has been shown to reduce both normal and elevated LDL-C concentrations, produce increases of variable magnitude in HDL-C, and modestly reduces VLDL-C and plasma triglycerides (TG).[1]

Mevacor is indicated for the following

- to reduce the risk of myocardial infarction, unstable angina, and coronary revascularization procedures in patients with average to moderately elevated total-C and LDL-C, and below average HDL-C
- to slow the progression of coronary atherosclerosis in patients with coronary heart disease
- an adjunct to diet for the reduction of elevated total-C and LDL-C levels in patients with primary hypercholesterolemia (Types IIa and IIb) and in adolescents (age 10 to 17) with Heterozygous Familial Hypercholesterolemia.

The recommended dosing range for adults is 10-80 mg/day in single or two divided doses. In adolescent patients, the recommended dosing range is 10-40 mg/day.

Merck is proposing to market Mevacor™ 20 mg tablet in the nonprescription setting for men 45 years and older and women 55 years of age and older, without clinical evidence of diabetes or cardiovascular disease, with LDL-C level between 130 mg/dL and 170 mg/dL, and one or more additional risk factors for coronary heart disease (CHD).

2.2 Currently Available Treatment for Indications

Mevacor (lovastatin) is a member of the statin class (HMG-CoA reductase inhibitors) used for the treatment of hyperlipidemias; other statins include atorvastatin, simvastatin, pravastatin, fluvastatin and rosuvastatin. This class of drugs is not currently approved in the US for nonprescription marketing.

2.3 Availability of Proposed Active Ingredient in the United States

Mevacor is widely available by prescription in the United States. Mevacor, originally marketed in 1987, has an estimated worldwide exposure of over 35 million patient-years as estimated by the applicant.

2.4 Important Issues With Pharmacologically Related Products

There are several important safety issues with HMG-CoA reductase inhibitors with respect to nonprescription marketing:

- Drug Interactions: Relative contraindications exist in patients taking specific concomitant medications such as potent CYP3A4 inhibitors (e.g., cyclosporine, erythromycin, clarithromycin, itraconazole), fibrates, niacin and various anti-fungal agents.
- Myopathy and Rhabdomyolysis: Statins are associated with an increased risk for myopathy ranging in severity from myalgias (muscle aches or weakness without CK elevation), to myositis (muscle symptoms with CK elevation), to rhabdomyolysis (muscle symptoms with creatine kinase levels > 10 x ULN in the presence of myoglobinuria). Myalgias comprise 25% of all statin-related adverse events with an incidence of 0 to 32% in randomized controlled trials. The estimated rate of myopathy with statin monotherapy is 0.025-0.5% and is dose-dependent. The incidence of rhabdomyolysis appears to be very low, on the order of 0.0042% per year. Factors known to enhance the odds for severe statin-induced myopathy include high vs. low statin dose, advanced age, carnitine palmityl transferase and myoadenylate deaminase deficiencies, heavy alcohol consumption, strenuous exercise, pre-existing latent myopathy and co-administration with niacin, cyclosporine, and fibrates, particularly gemfibrozil. Unlike other drugs in this class, P450 CYP3A4 extensively metabolizes simvastatin and lovastatin. Consequently, co-administration of these two statins with potent inhibitors of CYP3A4 may increase statin drug levels and confer an increase risk for myopathy.[2]
- Hepatic Effects: All statins can cause transient elevations of alanine aminotransferase (ALT). Increases in hepatic transaminase levels associated with statin use appear dose-related. The incidence of elevated serum transaminases from the statins as a class varies from 2% to 2.7 %.[3] Acute liver failure is estimated to occur at 0.2 per 100,000.[4]
- Pregnancy Category X: Lovastatin is contraindicated for use by pregnant or breastfeeding women. The Pregnancy Category X status was based on several preclinical studies. Two submissions to the prescription lovastatin NDA 19-643 (S-061 dated 06 June 2000 and 31 March 2004) requested to change lovastatin's Pregnancy Category from X to Category C. The request was denied due to insufficient data to support the change.
- Amyotrophic lateral sclerosis (ALS): The Office of Biostatistics and Office of New Drugs detected increased proportional reporting ratios for amyotrophic lateral sclerosis (ALS) for HMG-CoA reductase inhibitors (statins), with data mining signals for the two most commonly prescribed statins, atorvastatin and simvastatin. The extensive use of statins coupled with the dire consequences of being diagnosed with ALS led members of the Office of Surveillance and Epidemiology, the Office of Biostatistics, and the Divisions of Metabolism and Endocrinology Products and Neurology Products to conduct

an in-depth evaluation of the ALS data mining signal which was presented at the January 12, 2007, Regulatory Briefing (refer to Section 7.4 for additional information).

2.5 Presubmission Regulatory Activity

Other presubmission activities that have important effects on the current submission include:

NDA 21-213 originally was submitted on December 10, 1999 by Merck & Co, Inc. and Johnson & Johnson Consumer Pharmaceuticals Co. requesting the Agency's approval to market 10 mg strength tablets of lovastatin as an OTC drug product. This submission received a non-approvable (NA) action and the deficiencies are outlined in Section 1.3.1 of this review.

Supplement to NDA 19-643/S-075, submitted 01 July 2004, proposed to delete the baseline liver function testing (LFT) requirement (for doses less than 40mg) in the prescription Mevacor (lovastatin) package insert, discontinue the requirement for liver function testing at 6 and 12 weeks, and continue to recommend periodic liver function monitoring for patients with a prior history of liver transaminase elevations or when recent liver disease is suspected. Important points from that submission and review are:

- Data from large clinical trials and worldwide postmarketing safety reports supported a conclusion that lovastatin 20 mg has little to no hepatic risk in patients with normal liver tests at baseline. An analysis of 24 million patient-years of clinical experience with lovastatin reported that the rate of acute liver failure with lovastatin is approximately the same as the background rate of idiopathic acute liver failure, or 1 per 1.14 million patient-treatment years.[5] Furthermore, in the prescription setting, the label recommends that the health care provider consider a patient's history of confirmed or potential liver disease and obtain, if necessary, the laboratory tests prior to initiating drug therapy. Ultimately, the health care provider makes the clinical judgment whether that individual patient warrants baseline LFT monitoring.
- The data from AFCAPS and EXCEL showed that LFT monitoring at prespecified time points did not identify the majority of patients who will have elevations in liver transaminase levels nor was it predictive of future laboratory abnormalities. Therefore, patients should be monitored periodically at any time after the initiation of therapy if they develop signs or symptoms of liver disease.
- Merck relied on several small studies, primarily the Cornell University study in patients with chronic hepatitis C[6] and the Indiana University retrospective study of patients with abnormal elevated transaminase levels[7], to support their claim that baseline liver enzyme testing is unnecessary. The studies on statin use in patients with known chronic liver disease and with baseline elevated liver enzymes were reassuring that statins can be used safely in this population but inadequate to remove the recommendation to remove baseline testing altogether.

A joint advisory committee meeting involving members of the Non-prescription Drugs Advisory Committee (NDAC) and Endocrine and Metabolic Drugs Advisory Committee (EMDAC) was held on January 13 and 14, 2005, to discuss an application submitted to the Agency by Johnson and Johnson Merck Consumer Pharmaceutical Company (JJMCPC) for the over-the-counter availability of Mevacor® 20 mg. This was the second review cycle for the

proposed switch from Rx-only to OTC marketing status for lovastatin. The following is a summary of Dr. Parks's review of the resubmission and the outcome of the advisory committee meeting. Dr. Parks's review and NA memo is available in the Division File System (DFS) dated 24 August 2004.

The applicant modified the target patient population and nonprescription dose to address several of the deficiencies identified in the October 2000 non-approval letter. Mevacor 20 mg was now recommended for nonprescription use in a patient population that has 2 or more risk factors for heart disease and ≤ 20% 10-year risk of CHD. Treatment goal is an LDL-C < 130 mg/dL and based on lipid-altering efficacy data for lovastatin 20 mg, the majority of patients meeting the eligibility criteria for OTC Mevacor could achieve this goal with this dose of drug.

Efficacy:
The extrapolation of clinical benefit with lovastatin 20 mg to the proposed population was problematic as the analysis of AFCAPS/TexCAPS was a non-randomized comparison of treatment groups and the AFCAPS cohort did not accurately reflect the OTC population. Results from multiple clinical outcome trials with different statins provided additional evidence that cholesterol-lowering with statins did reduce the risk of cardiovascular disease. The committee agreed with DMEP's assessment that the applicant had proposed a patient population that merits therapy with lovastatin 20 mg, and that this dose would effectively lower cholesterol levels to a degree that would represent a clinical benefit.

Safety: Muscle Toxicity
With respect to muscle toxicity, the applicant presented sufficient data to conclude that the risk of myopathy and rhabdomyolysis at this dose is low. Drug-drug interactions are a concern as lovastatin drug levels may increase in the presence of potent CYP3A4 inhibitors. The applicant addressed this risk primarily through product labeling that reminds consumers to consult a physician if they are taking any prescription medication. The results of the actual use study revealed very few patients taking prohibited medications and the majority of these patients took appropriate action (i.e., discontinued lovastatin) or did not experience symptoms of muscle toxicity. DMEP and the advisory committee concluded that the risk of myopathy with lovastatin 20 mg is exceedingly low and is an appropriate dose for nonprescription use.

Safety: Hepatic Toxicity
Data from large clinical trials and worldwide postmarketing safety reports supported a conclusion that lovastatin 20 mg has little to no hepatic risk in patients with normal liver tests at baseline. The submission of one small study (n=42) in patients with chronic hepatitis C and a retrospective study of patients with abnormal elevated transaminase levels but no evidence of viral hepatitis prior to initiating statin therapy were concluded by DMEP to be inadequate to address whether patients with asymptomatic liver disease require monitoring before and during lovastatin therapy.

During the AC meeting, the applicant presented preliminary data from a cohort of patients enrolled in a Kaiser Permanente Healthcare plan. This study included patients with a variety of liver diseases including viral hepatitis who were treated with statins. A matched cohort of patients with similar liver diseases but who were not treated with statins was also evaluated.

These data were not submitted to the Agency, and were felt by DMEP to likely be relevant to the determination of whether LFT monitoring is necessary for nonprescription lovastatin 20 mg. Thus, despite the AC vote for removing any recommendation for LFT monitoring in the OTC setting, DMEP believed that a review of the Kaiser Permanente Study was needed before such a decision could be made. (This Kaiser Permanente Study is reviewed in Section 7.2 of this briefing document).

Safety: Pregnancy Risk
The CUSTOM actual use study revealed that 37% of women who selected to purchase and use the product were less than 55 years of age. While data were not collected on the fertility status of these women, 11% were younger than 45 years of age. Clearly, many in this age category could still be of childbearing potential. Given the theoretical risks to the fetus, the actual use study failed to demonstrate that women of childbearing potential would avoid using this product based on selection by age only.

As the prescription labeling for lovastatin will remain pregnancy category X because this product remains contraindicated for use during pregnancy, DMEP recommended revisions to the OTC product label to strongly discourage use by women of childbearing potential in the nonprescription setting. Such revisions would require comprehension testing to ensure consumer understanding of the risk of use in this category of patients.

Appropriateness of consumer management of hyperlipidemia
Unlike other medical conditions treated in the nonprescription setting, hypercholesterolemia is unique in that it is an asymptomatic condition for which treatment is lifelong. Unlike other OTC conditions, consumers must know the results of laboratory values (cholesterol values), risk factors for heart disease, and risk factors for drug-related side-effects to determine if they are ideal candidates for nonprescription lovastatin. After making the initial decision to use the product, the consumer must determine whether response to therapy is adequate. There are no symptoms to monitor. Determination of the adequacy of therapy is, again, based on obtaining bloodwork and the accurate interpretation of those results. Simultaneously, consumers must be aware of changing risk factors for both CHD and for drug adverse events. They need to be aware that a new diagnosis of diabetes mellitus, development of unstable angina, claudication, etc. or the initiation of therapy with a potent CYP3A4 inhibitor might unfavorably alter the risk-benefit equation of continuing nonprescription lovastatin. And, all these matters must be considered for the duration of therapy which is indefinite. In sum, hypercholesterolemia is a complex medical condition with challenges that must be met by not only making a safe and effective drug available OTC, but by ensuring that accuracy of diagnosis and adequacy of treatment is maintained while minimizing drug-related risks to the consumer.

The results of the CUSTOM study underscore the complexities of managing hypercholesterolemia in the nonprescription setting. As summarized in Dr. Shetty's review, (in DFS dated 24 Aug 2004), correct selection based on all labeled criteria was achieved by only 15.7% of the population that purchased and used the product. While this clinical program identified a treatment LDL-C goal to guide consumers on the adequacy of therapy, 37% (393/1059) of the purchase population did not obtain a follow-up LDL-C value. Of those who did obtain bloodwork (n=666), approximately one-fourth (n=160) did not adhere to label

instructions and continued therapy with nonprescription lovastatin despite not achieving LDL-C goals. Furthermore, nearly 30% of the purchase population had a baseline LDLC > 170 mg/dL (above the LDL-C eligibility criteria). Of these patients who had a follow-up LDL-C value, only 50% achieved an adequate reduction based on NCEP guidelines. In summary, the results of CUSTOM show that nonprescription treatment of hypercholesterolmia is not a tenable solution to the under-treatment of dyslipidemia in the general population.

The principal deficiency in this program remains poor consumer comprehension of the management of hypercholesterolemia. Approximately 57% of purchasers relied on physician advice to select the product. These results demonstrate the inability of consumers, on their own, to make decisions on the appropriateness of statin therapy. The large majority of Advisory Committee members were not persuaded by the data presented to them that Mevacor OTC could be used safely and effectively without physician guidance. There were concerns expressed in particular about whether patients could grapple with a theoretical benefit, since this is not a symptomatic treatment like many OTC drugs. In the end, the Advisory Committee voted 20 to 3 against approval for OTC marketing (verbatim minutes of the meeting are available at http://www.fda.gov/ohrms/dockets/ac/cder04.html#). Several AC members who voted against approving this application stated they would vote otherwise if a "behind-the-counter" marketing of the product were available. However, such a system does not exist in the United States and the decision to approve or not approve Mevacor® 20 mg for OTC use must be made within the confines of our current healthcare delivery system.

2.6 Other Relevant Background Information

Simvastatin is available without a prescription in the United Kingdom. Simvastatin (Zocor Heart Pro) 10 mg tablets were reclassified from prescription to non-prescription status (for sale in pharmacies for "behind-the-counter" marketing) in May, 2004. Simvastatin 10 mg is indicated for men 45 years and over and women 55 years and over with one or more risk factors for CHD.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Review pending

3.2 Animal Pharmacology/Toxicology

There were no preclinical data submitted to this NDA.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

In support of the current resubmission, requesting to switch Mevacor™ 20 mg from prescription to non-prescription status, the applicant provided results of two label comprehension studies, The Muscle Warning Comprehension Study (P088) and The Pivotal Label Comprehension study (P087), a non-drug, self-selection study entitled "Self Evaluation of Lovastatin to Enhance Cholesterol Treatment (SELECT, P086) and proposed OTC labeling. No new clinical data were provided. Safety was assessed with an integrated summary of safety, published literature and a retrospective cohort database study entitled "Study of potential hepatotoxicity of lovastatin in the Northern California Kaiser Permanente liver disease population".

4.2 Tables of Clinical Studies

Not applicable for this review.

4.3 Review Strategy

The label comprehension studies and SELECT will be reviewed by the Division of Nonprescription Clinical Evaluation, Office of Nonprescription Products. The safety evaluation will be reviewed in this document with consults from the Office of Surveillance and Epidemiology.

4.4 Data Quality and Integrity

Not applicable as this document does not contain new clinical studies.

4.5 Compliance with Good Clinical Practices

Not applicable as this document does not contain new clinical studies.

4.6 Financial Disclosures

The applicant has submitted the findings from three literature studies to address the concern if LFT monitoring would be necessary in consumers with baseline LFT abnormalities to ensure the safe use of this product in the non-prescription setting. The applicant was asked if they had provided any financial or other support to these studies:

a. Reference 4080
Avins AL, Manos MM, Ackerson L, Zhao W, Murphy R, Levin TR. Study of potential hepatotoxicity of lovastatin in the Northern California Kaiser Permanente liver disease population: final report.

Response: Yes, the Sponsor provided financial support to Kaiser Permanente Northern California (KPNC) for the conduct of this retrospective study. Personnel at KPNC

performed the chart review and data analysis and prepared the final report. Abstracts and publications of this study are co-authored by KPNC and Merck.

b. Reference 4045/4083
Vuppalanchi R, Teal E, Chalasani N. Patients with elevated baseline liver enzymes do not have higher frequency of hepatotoxicity from lovastatin than those with normal baseline Liver enzymes. Am J Med Sci 2005;329(2):62-5.

Response: No financial or other support was provided by the Sponsor.

c. Reference 4049
Browning JD. Statins and hepatic steatosis: perspectives from the Dallas heart study. Hepatology 2006;44(2):466-71.

Response: No financial or other support was provided by the Sponsor.

5 CLINICAL PHARMACOLOGY

No new Clinical Pharmacology data were submitted with this application.

6 INTEGRATED REVIEW OF EFFICACY

No new efficacy data were submitted with this application. Lipid-altering efficacy of lovastatin 20 mg was summarized from 3 different clinical sources: EXCEL, AFCAPS/TexCAPS, and CUSTOM. These three studies involved different patient populations, study designs, and treatment approaches and differences in efficacy were not unexpected. This was presented at the January 2005 Advisory Committee which is summarized below:

6.1 EXCEL

EXCEL was a randomized, double-blind, placebo-controlled study evaluating 5 treatment groups: lovastatin 20 mg q pm; lovastatin 40 mg q pm; lovastatin 20 mg bid; lovastatin 40 mg bid; and placebo. There were 1,642 patients randomized to the lovastatin 20 mg daily group. The EXCEL cohort included patients with higher baseline cholesterol levels (mean LDL 180 mg/dL± 21) than AFCAPS/TexCAPS (mean LDL 150 mg/dL± 21) or CUSTOM (mean LDL 157 mg/dL± 42). By Week 48, 31% of the lovastatin 20 mg daily treatment group had achieved an LDL-C < 130 mg/dL and the mean percent change from baseline was –24%.

6.2 AFCAPS/TexCAPS

AFCAPS/TexCAPS randomized 6,605 patients to lovastatin 20 mg daily (n=3304) or placebo (n=3301). Lovastatin dose was titrated to 40 mg daily if at Week 18, LDL-C levels remained > 110 mg/dL. Approximately half of the lovastatin-treatment group was titrated to the 40 mg dose. The applicant presented data at Week 18 which represented only lipid-altering efficacy at the 20 mg daily dose. These data were available from only one of two sites which analyzed lipids

during this clinical trial. Lipid-altering data at 1 year in only those patients remaining on the lovastatin 20 mg dose were also evaluated. The mean percent change in LDL-C from baseline in both analyses was approximately – 24.0%.

A post-hoc analysis of the AFCAPS/TexCAPS database was undertaken by the applicant to estimate the clinical benefit with lovastatin 20 mg to the proposed non-prescription population. The applicant's analysis suggested that the Number Needed to Treat (NNT) over a 6-year period to avoid one CHD event was 28.

Dr. Parks, in her medical team leader DMEP review, stated the following:
While it is logical to assume that an individual taking nonprescription lovastatin 20 mg and has some reduction in cholesterol levels will also lower his/her risk of heart disease, a numerical assignment of risk reduction based on AFCAPS/TexCAPS is not possible. The estimates of risk reduction in the Mevacor-OTC eligible patient population are based on analyses of subpopulations in AFCAPS/TexCAPS that had an average treatment follow-up period of 5 years. During this follow-up period, dietary reinforcement and other risk factor modifications were provided to study participants. Study visits occurred every 6 weeks for the first 48 weeks of the study and every 6 months thereafter. The true risk reduction for nonprescription lovastatin use must factor in effectiveness of therapy (i.e., adequate LDL-lowering), long-term adherence to therapy and therapeutic lifestyle interventions, and appropriate management of other CHD risk factors. To date, the Agency only has 6 months of data for Mevacor 20 mg in the proposed OTC population.

Dr. Mele, in her biometrics review[8], presented the Kaplan-Meier estimates from the FDA review of AFCAPS/TEXCAPS and showed that the NNT was 48 over a 5-year treatment period. She further notes that there were only two centers in AFCAPS/TEXCAPS and one center (with 43% of the patients) had a maximum follow-up of 5.1 years. A small number of patients completed 6 years of treatment. Dr. Follman, the statistician on the DMEDP/OTC advisory committee, requested information regarding the five and six year NNT values. The applicant provided information that the NNT was 43 (95% CI: 26, 120) over 5 years and 25 (95% CI: 17, 51) over 6 years. Dr. Mele commented that this information provided by Merck clearly shows the unstableness of the NNT with large differences between the 5 year and 6 year calculations. About half of the OTC eligible population (from the AFCAPS database) completed 5 years on study and about 1/5 completed 6 years on study. Dr Mele concluded that the applicant's NNT estimates were not acceptable and underestimates the NNT.

6.3 CUSTOM

The applicant conducted one actual use study entitled: A Consumer Use Study of OTC MEVACOR™ (CUSTOM): A 6-Month Consumer Behavior Study of the MEVACOR™ OTC Self-Management System**.** The following summary is based on Dr. Daiva Shetty's review in DFS dated 24 Aug 2004.

The objectives of the actual use study was to determine if the MEVACOR™ OTC Self-

Management System enables consumers to appropriately manage elevated cholesterol levels and to assess the safety and tolerability of MEVACOR™ OTC in a population who chooses to self-medicate.

Study Results
Self-Selection Assessment
According to the proposed label, there were 4 conditions that determine correctness of the self-selection, and the hierarchy of a thought process that consumers have to go through when looking at the label is as follows:
1. Age: **only** for men 45 years or older or women 55 years or older,
plus
2. LDL-C level **only** between 130 and 170 mg/dL,
plus
3. One or more of the following risk factors for CHD:
Smoking
High blood pressure
Family history of CHD
HDL-C 1 to 39 mg/dL
plus
4. Absence of conditions that may put the user at increased risk of an adverse experience (liver disease, high triglycerides, history of statin-induced muscle pain)

Out of the 430 women who purchased and used the study drug, 63% (269/430) met the age criteria (> 55 years), of those 100 had baseline LDL-C between 130 and 170 mg/dL, and 16% (69/430) had one or more risk factors for CHD.

Male Users were older and had a higher number of risk factors for CHD. Out of the 629 male Users, 84% (530/629) met the age criteria (> 45 years), of those 181 had baseline LDL-C between 130 and 170 mg/dL, and 22% (137/629) had one or more CHD risk factor.

The number of study participants fitting all 4 of these criteria was low: only 110 (10%) out of the 1059 Users. The majority of these (N = 77) were men. Only 8% (33/430) of the women Users in the study met these criteria.

Furthermore, according to the applicant's Data Analysis Plan, 484 participants initially self-selected correctly for Mevacor 20 mg according to the label criteria. However, only 14% (68 participants) initially self-selected correctly according to the label criteria *without* a physician's intervention.

Compliance with the Follow-up Cholesterol Test
Only 63% (666/1059) of the Users had a follow-up test during the 6 months of the study; 346 (32.7%) had it within the specified time interval of 4 to 12 weeks.

LDL-C Reduction in User Population
The median reduction in LDL-C achieved in the population who used Mevacor 20 mg OTC was 20.6%. Further reduction, 25.2%, was observed in the cohort of 243 Users that fasted at baseline

and at the end of study. A total of 282 (26.6%) Users achieved the LDL-C goal of < 130 mg/dL within 4 to 12 weeks. The percentage of Users achieving the LDL-C goal of <130 mg/dL by the end of the 6-month study was 39.7% (349/878).

6.4 LDL Cholesterol Label Paradigm vs. Total Cholesterol Label Paradigm

In the October 2000 "Not Approved" action letter on Merck's nonprescription lovastatin application, one of the specific deficiencies of the application was that Current National Cholesterol Education Program (NCEP) Guidelines were not incorporated in the OTC treatment paradigm.

In 2001 NCEP published its third Executive Summary on the management of hyperlipidemia in adults (Adult Treatment Panel III or ATP III)[9] and proposed new treatment guidelines. 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 CV event over a 10-year period. ATP-III uses Framingham point scores in estimating these 10-year CHD risks, with age, total cholesterol, smoking status, HDL-C, and blood pressure contributing to the total score. These 10-year CHD risk estimates determine whether an individual falls into one of 4 categories:

- CHD or CHD risk equivalents (10-yr risk > 20%)
- 2+ risk factors for heart disease (10-yr risk 10-20%)
- 2+ risk factors for heart disease (10-yr risk < 10%)
- none to 1 risk factor for heart disease

In July 2004, members of the Coordinating Committee of the National Cholesterol Education Program published updates to NCEP ATP-III based on the results of 5 major clinical outcomes trials published after May 2001.[10] These revised recommendations stated that in individuals with very high risk for a CV event, an LDL-C goal of < 70 mg/dL is a therapeutic option.

Individuals with diabetes but without clinically evident CHD and those with other clinical forms of atherosclerotic disease (e.g., peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease) have equivalent status to those individuals with established CHD. Risk factors for heart disease that may modify LDL-C goals include smoking, HTN, HDL < 40 mg/dL, family history of premature CHD, and age.

The NCEP ATP-III Guidelines also identified other lipid parameters beyond LDL-C that contributed to the atherosclerotic process that required treatment intervention if abnormal. Specifically, elevated serum triglyceride (TG) levels may contribute to risk for CHD, and the optimal level should be < 150 mg/dL. In patients who have reached their LDL-C goal but whose TGs were > 200 mg/dL, a secondary target of therapy is non-HDL-C (this comprises the pool of atherogenic, cholesterol-ester containing, apo B lipoproteins) with the goal being set 30 mg/dL higher than that for LDL-C. In many instances, this secondary target of therapy must be addressed with additional lipid-altering therapies (e.g., fibrates, niacin).

The following table summarizes the treatment approach for hypercholesterolemia.

Table 6.4.1 ATP III LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories and Proposed Modifications Based on Recent Clinical Trial Evidence[11]

Risk Category	LDL-C Goal	Non-HDL Goal	Initiate TLC	Consider Drug Therapy**
High risk: **CHD* or CHD risk equivalents† (10-year risk >20%)**	<100 mg/dL (optional goal: <70 mg/dL)‼	< 130 mg/dL (optional goal: <100 mg/dL)	≥100 mg/dL#	≥100 mg/dL†† (<100 mg/dL: consider drug options)**
Moderately high risk: **2+ risk factors‡ (10-year risk 10% to 20%)**	<130 mg/dL¶	< 160 mg/dL	≥130 mg/dL#	≥130 mg/dL (100–129 mg/dL; consider drug options)‡‡
Moderate risk: **2+ risk factors‡ (10-year risk <10%)**	<130 mg/dL	< 160 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower risk: **0–1 risk factor**	<160 mg/dL	< 190 mg/dL	≥160 mg/dL	≥190 mg/dL (160–189 mg/dL: LDL-lowering drug optional)

*CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.
†CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery]), diabetes, and 2+ risk factors with 10-year risk for hard CHD >20%.
‡Risk factors include cigarette smoking, hypertension (BP ≥140/90 mm Hg or on antihypertensive medication), low HDL cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years of age; CHD in female first-degree relative <65 years of age), and age (men ≥45 years; women≥ 55 years).
§Almost all people with zero or 1 risk factor have a 10-year risk <10%, and 10-year risk assessment in people with zero or 1 risk factor is thus not necessary.
‼Very high risk favors the optional LDL-C goal of <70 mg/dL, and in patients with high triglycerides, non-HDL-C <100 mg/dL.
¶Optional LDL-C goal <100 mg/dL.
#Any person at high risk or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for therapeutic lifestyle changes to modify these risk factors regardless of LDL-C level.
**When LDL-lowering drug therapy is employed, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.
††If baseline LDL-C is <100 mg/dL, institution of an LDL-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high triglycerides or low HDL-C, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.
‡‡For moderately high-risk persons, when LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of available clinical trial results.

The population defined by Mevacor Daily targets consumers without CHD who are at intermediate risk of a CHD event over 10 years. This approximately corresponds to moderate risk and moderately high risk in Table 6.4.1. Based on NCEP ATP III guidelines, LDL-C goal for the OTC-eligible population is < 130 mg/dL. Drug therapy should be considered after therapeutic lifestyle changes fail to achieve this goal (or < 160 mg/dL if 10-yr risk is < 10%).

The applicant states that individuals taking prescription cholesterol medications, LDL-C 171 to 400 mg/dL (LDL paradigm) or TC 241 to 700 mg/dL (TC paradigm), diabetes, CHD, or a history of stroke are not candidates for OTC lovastatin. These patients were excluded from nonprescription lovastatin use because their 10-year CHD risk would unlikely be adequately treated with lovastatin 20 mg and more aggressive management of other risk factors would require direct physician management.

There were two label paradigms tested in SELECT, LDL-C and Total-C.

LDL Cholesterol Label Paradigm

- *LDL cholesterol range is between 130 to 170 mg/dL*
- *Both males and females must have an additional risk factor in addition to meeting the age criteria*

Consumers are considered eligible for nonprescription lovastatin if they meet the following criteria on the product label:
1. males 45 yrs or older or females 55 years or older; and
2. LDL-C between 130 and 170 mg/dL; and
3. having at least one of the following risk factors
   - high blood pressure or taking medication to control your blood pressure
   - family history of heart disease: father/brother before age 55 or mother/sister before age 65
   - smoker OR
   - low HDL-C between 1 and 39 mg/dL

The population defined by the LDL-C label is largely consistent with ATP III Guidelines and targets consumers without CHD who are at intermediate risk of a CHD event.

Consumers are instructed to check a fasting cholesterol after 6 weeks “to see if your LDL “bad” cholesterol has reached a healthy level:

- LDL “bad” cholesterol 1 to 129. It’s working, keep taking it daily and test your cholesterol once a year
- LDL “bad” cholesterol 130 to 400. This product may not be strong enough for you. Talk to a doctor about using a prescription cholesterol medicine”

The treatment goal defined by the LDL-C label is consistent with ATP III Guidelines as subjects with moderate risk and moderately high risk have a treatment goal of LDL-C < 130 mg/dL.

Total Cholesterol Label Paradigm

The applicant states that this label paradigm parallels the NCEP ATP III Guidelines by targeting consumers at risk of CHD and is similar to the LDL label paradigm risk factor distribution. According to the applicant, this label paradigm may be more “consumer-friendly” since consumers are generally more aware of their total cholesterol than their LDL cholesterol; additionally, the “borderline elevated” total cholesterol range 200 to 240 mg/dL may be familiar to many consumers and may be less confusing to consumers when deciding if MEVACOR™ Daily is appropriate for them.

Guidelines for lipid lowering therapy:

- *Total cholesterol range is between 200 to 240 mg/dL*
- *Men meeting the age criteria do not need a risk factor.*

Consumers are considered eligible for nonprescription lovastatin if they meet the following criteria on the product label:
1. males 45 yrs or older or females 55 years or older; and
2. TC between 200 and 240 mg/dL; and
3. Women must also have HDL-C between 1 and 59
3. Women must have at least one of the following risk factors
   - high blood pressure or taking medication to control your blood pressure
   - family history of heart disease: father/brother before age 55 or mother/sister before age 65
   - smoker OR
   - low HDL-C between 1 and 39 mg/dL

Women
In the TC label paradigm, women must be able to select the correct age group, the correct total cholesterol range, the correct HDL-C 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-C, it is likewise reasonable to accept that HDL-C is a difficult concept for the consumer to understand and utilize in determining treatment eligibility. However, if a woman is able to select correctly, she is likely to meet the criteria that are set forth in the NCEP ATP III guidelines.

Consumers (women and men) are instructed to check a fasting cholesterol after 6 weeks "to see if your Total cholesterol has reached a healthy level:

- Total cholesterol 1 to 199. It's working, keep taking it daily and test your cholesterol once a year
- Total cholesterol 200 to 700. This product may not be strong enough for you. Talk to a doctor about using a prescription cholesterol medicine"

The treatment goal defined by the TC label is not consistent with ATP III Guidelines as subjects with moderate risk and moderately high risk have a treatment goal of LDL-C < 130 mg/dL and it is not based on TC.

Whether a woman self-selecting for treatment based on the TC label can appropriately assess her treatment goal which, as per NCEP ATP III guidelines, is based on an LDL-C target was not explored in this submission.

Men
In the TC label paradigm, men must be able to select the correct age group and the correct total cholesterol range. The correct HDL-C range and one of the appropriate risk factors is not part of the selection criteria for this paradigm for men. While this label is simpler to understand than the LDL-C label, the male population defined by the TC label is not consistent with ATP III

Guidelines and targets male consumers without CHD who are at low as well as high risk of a CHD event. If a man does not have one of the risk factors described in NCEP ATP III, namely cigarette smoking, hypertension (BP ≥140/90 mm Hg or on antihypertensive medication), low HDL cholesterol (<40 mg/dL), or family history of premature CHD (CHD in male first-degree relative <55 years of age; CHD in female first-degree relative <65 years of age), then he is in the lower risk category and his LDL-C treatment goal is <160 mg/dL, not <130 mg/dL. To further illustrate, a 45-year old man with no cardiac risk factors, TC=200 mg/dL, TG=100 mg/dL and HDL=50 mg/dL would have an estimated LDL-C of 130 mg/dL and a 4% 10-year risk for CHD. He would not meet the criteria for drug therapy based on NCEP ATP III but would meet the criteria for Mevacor Daily based on the TC label paradigm. On the other hand, a 50-year old man who smokes, has hypertension, and a positive family history of heart disease with a TC=240 mg/dL, TG=100 mg/dL and HDL=20 mg/dL would have an estimated LDL-C of 200 mg/dL and ≥ 30% 10-year risk for CHD. He would meet the selection criteria for Mevacor Daily using the TC label but not by the LDL-C label. With optimal effect of Mevacor Daily, his LDL-C would decrease to ~152 mg/dL and his TC to ~192 mg/dL. He would meet treatment goal according to the TC label but not according to NCEP ATP III guidelines.

Again, whether a man self-selecting for treatment based on the TC label can appropriately assess his treatment goal which, as per NCEP ATP III guidelines, is based on an LDL-C target was not explored in this submission.

This reviewer believes that the TC label paradigm neither parallels the NCEP ATP III Guidelines in selecting consumers at moderate to moderately-high risk of CHD nor reflects the Guidelines for treatment goals--which is based on LDL goals. While this reviewer agrees with the applicant that total cholesterol is an easier concept to understand, we are still left with the issue that the consumer must understand LDL values, and at times HDL values, to correctly determine when it is appropriate to self-treat and when to seek a health care provider's guidance. Overall, the LDL-C label more consistently parallels the NCEP ATP III guidelines as compared to the TC label.

CHD Risk <5% by Gender for LDL-C and TC Paradigm

As shown in Table 6.4.2 for females and Table 6.4.3 for males, the gender distribution of the 536 participants with CHD risk <5% who provided a purchase decision was 409 females (76.3%) and 127 males (23.7%).

**Table 6.4.2 Comparison of Self-Assessment /Purchase Decision by Paradigm
Female Participants with CHD Risk <5%**

	LDL-C Paradigm†	Total-C Paradigm†	Combined Paradigms†
Self-Assessment: No. of Participants with CHD risk <5%	194	204	398
SA = Yes	42 (21.6%)	41 (20.1%)	83 (20.9%)
SA = No	139 (71.6%)	153 (75.0%)	292 (73.4%)
SA = Other	13 (6.7%)	10 (4.9%)	23 (5.8%)
Purchase Decision: No. of Participants with CHD risk <5%	199	210	409
PD = Yes	42 (21.1%)	46 (21.9%)	88 (21.5%)
PD = No	157 (78.9%)	164 (78.1%)	321 (78.5%)

† Participants with missing SA or PD decision, participants with missing data, participants whose eligibility could not be determined due to a data collection issue, and protocol violators are excluded.
CHD = Coronary Heart Disease; PD = Purchase Decision; SA = Self Assessment

Data Source: Applicant's Table 11-25

The proportion of female participants who decided not to buy (PD=No) was similar for this CHD risk <5% group for females in both the LDL-C and TC label paradigm (157/199, 79% for LDL-C and 164/210, 78% for TC).

Likewise, the proportion of female participants who decided to buy (PD=Yes) was similar for this CHD risk <5% group for females in both the LDL-C and TC label paradigm (42/199, 21% for LDL-C and 46/210, 22% for TC).

**Table 6.4.3
Comparison of Self-Assessment /Purchase Decision by Paradigm
Male Participants with CHD Risk <5%**

	LDL-C Paradigm†	Total-C Paradigm†	Combined Paradigms†
Self-Assessment: No. of Participants with CHD risk < 5%	66	56	122
SA = Yes	13 (19.7%)	17 (30.4%)	30 (24.6%)
SA = No	52 (78.8%)	38 (67.9%)	90 (73.8%)
SA = Other	1 (1.5%)	1 (1.8%)	2 (1.6%)
Purchase Decision: No. of Participants with CHD risk < 5%	68	59	127
PD = Yes	10 (14.7%)	17 (28.8%)	27 (21.3%)
PD = No	58 (85.3%)	42 (71.2%)	100 (78.7%)

† Participants whose eligibility could not be determined due to a data collection issue and protocol violators are excluded.
CHD = Coronary Heart Disease; PD = Purchase Decision; SA = Self Assessment.

Data Source: Applicant's Table 11-26

The proportion of male participants with a CHD risk <5% who decided not to buy (PD=No) was higher for the LDL-C compared to the TC label paradigm (58/68, 85% for LDL-C and 42/59, 71% for TC).

In contrast, the proportion of male participants with a CHD risk <5% who decided to buy (PD=Yes) was lower for the LDL-C compared to the TC label paradigm (10/68, 15% for LDL-C and 17/59, 29% for TC). This doubling of the incidence of men with low CHD who selected to purchase Mevacor may be due to the entry criteria for the TC label that allows men with only

one CHD risk factor, thus, by definition, are at low CHD risk and may not be recommended for statin therapy.

Eligibility Assessment: TC vs. LDL label paradigm and Gender

Table 6.4.4
Classification of Label Eligibility vs. Self-Assessment Decision LDL-C Label Paradigm: (Male Only)

	Self-Assessment vs. Eligibility Per Label (N=325)[†,‡]	
	Correct vs. EA 220(67.7%)	Incorrect vs. EA 105(32.3%)
Participant Response	**n**	**n**
Yes	27	97
No	193	8

† Excludes 1 participant with missing Self Assessment. and 18 participants with missing data, cholesterol test after Self Assessment or Purchase Decision, and protocol violators.
‡ Eighteen participants who gave a response that was classified as "other" to the self-assessment question are also excluded.
EA = Eligibility assessment.

Data Source: Applicant's Table 14-26

LDL-C paradigm (Male Only):

- Of the 220 men that made a correct self-assessment decision: 27/220 (12%) made a correct self-assessment decision that Mevacor Daily was appropriate for me and 193/220 (88%) made a correct self-assessment decision that Mevacor Daily was not appropriate for me.

- Of the 124 men that decided "Mevacor Daily is appropriate for me": 27/124 (22%) were correct and 97/124 (78%) were incorrect.

Table 6.4.5
Classification of Label Eligibility vs. Self-Assessment Decision LDL-C Label Paradigm: (Female Only)

	Self-Assessment vs. Eligibility Per Label (N=337)[†,‡]	
	Correct vs. EA 253(75.1%)	Incorrect vs. EA 84(24.9%)
Participant Response	**n**	**n**
Yes	7	83
No	246	1

† Excludes 27 participants with missing data, cholesterol test after Self Assessment or Purchase Decision, and protocol violators.
‡ Twenty-eight participants who gave a response that was classified as "other" to the self-assessment question are also excluded.
EA = Eligibility Assessment.

Data Source: Applicant's Table 14-27

LDL-C paradigm (Female Only):

- Of the 253 women that made a correct self-assessment decision: 7/253 (3%) made a correct self-assessment decision that Mevacor Daily was appropriate for me and 246/253

(88%) made a correct self-assessment decision that Mevacor Daily was not appropriate for me.

- Of the 90 women that decided "Mevacor Daily is appropriate for me": 7/90 (8%) were correct and 83/90 (92%) were incorrect.

Table 6.4.6.
Classification of Label Eligibility vs. Self-Assessment Decision Total-C Label Paradigm: (Male Only)

	Self-Assessment vs. Eligibility Per Label (N=319)†,‡	
	Correct vs. EA 221(69.3%)	Incorrect vs. EA 98(30.7%)
Participant Response	n	n
Yes	53	92
No	168	6

† Excludes 26 participants with missing data, cholesterol test after Self Assessment or Purchase Decision, and protocol violators.
‡ Sixteen participants who gave a response that was classified as "other" to the self-assessment question are also excluded.
EA = Eligibility Assessment

Data Source: Applicant's Table 14-28

TC paradigm (Male Only):

- Of the 221 men that made a correct self-assessment decision: 53/221 (24%) made a correct self-assessment decision that Mevacor Daily was appropriate for me and 168/221 (76%) made a correct self-assessment decision that Mevacor Daily was not appropriate for me.

- Of the 145 men that decided "Mevacor Daily is appropriate for me": 53/145 (37%) were correct and 92/145 (63%) were incorrect.

Table 6.4.7
Classification of Label Eligibility vs. Self-Assessment Decision Total-C Label Paradigm: (Female Only)

	Self-Assessment vs. Eligibility Per Label (N=345)†,‡	
	Correct vs. EA 259(75.1%)	Incorrect vs. EA 86(24.9%)
Participant Response	n	n
Yes	13	84
No	246	2

† Excludes 1 participant with missing self-assessment and 17 participants with missing data, cholesterol test after Self Assessment or Purchase Decision, and protocol violators.
‡ Twenty-one participants who gave a response that was classified as "other" to the self assessment question are also excluded.
EA = Eligibility Assessment

Data Source: Applicant's Table 14-29

TC paradigm (Female Only):

- Of the 259 women that made a correct self-assessment decision: 13/259 (5%) made a correct self-assessment decision that Mevacor Daily was appropriate for me and 246/259 (95%) made a correct self-assessment decision that Mevacor Daily was not appropriate for me.

- Of the 97 women that decided "Mevacor Daily is appropriate for me": 13/97 (13%) were correct and 84/97 (87%) were incorrect.

Conclusion on Eligibility Assessment:
Men performed better with the total cholesterol label, of the 145 men that decided "Mevacor Daily is appropriate for me", 37% were correct and 63% were incorrect as compared to the LDL label where, of the 124 men that decided "Mevacor Daily is appropriate for me", only 22% were correct and 78% were incorrect.

Women also performed better with the total cholesterol label, of the 97 women that decided "Mevacor Daily is appropriate for me", 13% were correct and 87% were incorrect as compared to the LDL label where, of the 90 women that decided "Mevacor Daily is appropriate for me", only 8% were correct and 92% were incorrect.

It is important to note that with either label, of the consumers that stated Mevacor was appropriate for me, the percentage of correct responses was a sobering 8 to 37%.

Purchase Decision: TC vs. LDL label paradigm and Gender

Table 6.4.8
Classification of Label Eligibility vs. Purchase Decision LDL-C Label Paradigm: (Male Only)

	Purchase Decision vs. Eligibility Per Label (N=352)†		
	Correct Purchase Decision 271(77.0%)		Incorrect Purchase Decision 81(23.0%)
	Eligible Per Label	Not Eligible Per Label	Not Eligible Per Label
Participant Purchase Decision	n	n	n
Yes	23		81
No	14	234	

† Excludes 3 participants with missing purchase decision and 7 participants with missing data, cholesterol test after Purchase Decision, and protocol violators.

Data Source: Applicant's Table 14-30

LDL-C paradigm (Male Only):

- Of the 271 men that made a correct purchase decision: 23/271 (8%) made a correct purchase decision that Mevacor Daily was appropriate for me.

- Of the 104 men that decided to purchase Mevacor Daily: 23/104 (22%) were correct and 81/104 (78%) were incorrect.

Table 6.4.9
Classification of Label Eligibility vs. Purchase Decision LDL-C Label Paradigm: (Female Only)

	Purchase Decision vs. Eligibility Per Label (N=380)†		
	Correct Purchase Decision 294 (77.4%)		Incorrect Purchase Decision 86 (22.6%)
Participant Purchase Decision	Eligible Per Label	Not Eligible Per Label	Not Eligible Per Label
	n	n	n
Yes	6		86
No	3	285	

† Excludes 12 participants with missing data, cholesterol test after Purchase Decision, and protocol violators.

Data Source: Applicant's Table 14-31

LDL-C paradigm (Female Only):

- Of the 294 women that made a correct purchase decision: 6/294 (2%) made a correct purchase decision that Mevacor Daily was appropriate for me.

- Of the 92 women that decided to purchase Mevacor Daily: 6/92 (7%) were correct and 88/92 (93%) were incorrect.

Table 6.4.10
Classification of Label Eligibility vs. Purchase Decision Total-C Label Paradigm: (Male Only)

	Purchase Decision vs. Eligibility Per Label (N=349)†		
	Correct Purchase Decision 262 (75.1%)		Incorrect Purchase Decision 87 (24.9%)
	Eligible Per Label	Not Eligible Per Label	Not Eligible Per Label
Participant Purchase Decision	n	n	n
Yes	46		87
No	19	197	

† Excludes 12 participants with missing data, cholesterol test after Purchase Decision, and protocol violators.

Data Source: Applicant's Table 14-32

TC paradigm (Male Only):

- Of the 262 men that made a correct purchase decision: 46/262 (18%) made a correct purchase decision that Mevacor Daily was appropriate for me.

- Of the 133 men that decided to purchase Mevacor Daily: 46/133 (35%) were correct and 87/133 (65%) were incorrect.

Table 6.4.11
Classification of Label Eligibility vs. Purchase Decision Total-C-Label Paradigm: (Female Only)

	Purchase Decision vs. Eligibility Per Label (N=376)†		
	Correct Purchase Decision 295 (78.5%)		Incorrect Purchase Decision 81 (21.5%)
	Eligible Per Label	Not Eligible Per Label	Not Eligible Per Label
Participant Purchase Decision	n	n	n
Yes	9		81
No	7	279	

† Excludes 8 participants with missing data, cholesterol test after Purchase Decision, and protocol violators.

Data Source: Applicant's Table 14-33

TC paradigm (Female Only):

- Of the 295 women that made a correct purchase decision: 9/295 (3%) made a correct purchase decision that Mevacor Daily was appropriate for me.

- Of the 90 women that decided to purchase Mevacor Daily: 9/90 (10%) were correct and 81/90 (90%) were incorrect.

Conclusion on Purchase Decision:
Men performed better with the total cholesterol label, of the 133 men that decided to purchase Mevacor Daily, 35% were correct as compared to the LDL label where, of the 104 men that decided to purchase Mevacor Daily, only 22% were correct.

Women performed better with the total cholesterol label, of the 90 women that decided to purchase Mevacor Daily, 10% were correct as compared to the LDL label where, of the 92 women that decided to purchase Mevacor Daily, only 7% were correct.

Similar to the self-assessment decision, of the consumers that wanted to purchase Mevacor, the percentage of correct responses was a sobering 7 to 35%.

6.5 Efficacy Conclusion

Notwithstanding the flaws of the analysis of AFCAPS/TexCAPS, this analysis did provide the best assessment of the benefits of Mevacor 20 mg for nonprescription use to effectively lower cholesterol levels to a degree that would represent a clinical benefit.

If Mevacor Daily is approved for non-prescription use, this reviewer recommends that information be placed on the package labeling that describes an estimate of clinical benefit for the consumer, such as:

> Mevacor Daily, if taken every day and as directed by the label, can reduce the chance that you will experience cardiac death, heart attack, or unstable angina (chest pain at rest) over the next 5 years: 72 people out of 1000 experienced these symptoms on placebo compared to 51 people out of 1000 who experienced these symptoms on Mevacor Daily[1]*

This reviewer approached this submission using the LDL-C label paradigm. If the applicant proposes that the Total Cholesterol (TC) label paradigm should be the label for MEVACOR™ Daily, they must provide evidence that demonstrates that the eligibility criteria in that label (for both men and women) target the same CHD risk population as the LDL-C paradigm. Also, they must provide evidence that consumers using the TC label can appropriately assess their treatment goal which, as per NCEP ATP III guidelines, is based on an LDL-C target.

7 INTEGRATED REVIEW OF SAFETY

There are several important safety issues with lovastatin, and HMG-CoA reductase inhibitors in general, with respect to nonprescription marketing:

- Muscle effects and Drug Interactions: Statins are associated with an increased risk for myopathy ranging in severity from myalgias to rhabdomyolysis. Unlike other drugs in this class, P450 CYP3A4 extensively metabolizes simvastatin and lovastatin. Relative contraindications exist in patients taking specific concomitant medications such as potent CYP3A4 inhibitors (e.g., cyclosporine, erythromycin, itraconazole), fibrates, niacin and various anti-fungal agents. Consequently, co-administration of these two statins with potent inhibitors of CYP3A4 or large amounts of grapefruit juice may increase statin drug levels and confer an increase risk for myopathy.[12]
- Hepatic Effects: Data from large clinical trials and worldwide postmarketing safety reports supported a conclusion by DMEP and the Advisory Committee in 2005 that lovastatin 20 mg has little to no hepatic risk in patients with normal liver tests at baseline. However, there was insufficient evidence presented in 2005 to recommend that no LFT monitoring would be necessary in consumers with baseline LFT abnormalities for the safe use of this product in the non-prescription setting.
- Pregnancy Category X: Lovastatin is contraindicated for use by pregnant or breastfeeding women. The Custom actual use study revealed that 37.4% of women who selected to purchase and use the product were less than 55 years of age and that 11% were younger than 45 years of age. Given the theoretical risks to the fetus, the actual use study failed to

1 Mele J Biometrics Memo for Mevacor OTC, NDA 21-213,Table 2, in DFS dated 24 Aug 2004
* The extrapolation of clinical benefit with this 20 mg dose in the proposed OTC population will need to be adjusted to account for the difference in the AFCAPS/TexCAPS cohort which was titrated up to a 40 mg dose to attain a lower LDL-C target of therapy (<110 mg/dL).

demonstrate that women of childbearing potential would avoid using this product based on selection by age only. DMEP recommended revisions to the OTC product label to strongly discourage use by women of childbearing potential in the nonprescription setting and recommended comprehension testing to ensure consumer understanding of the risk of use in this category of patients.

- Amyotrophic lateral sclerosis (ALS): The Office of Biostatistics and Office of New Drugs have detected increased proportional reporting ratios for amyotrophic lateral sclerosis (ALS) for HMG-CoA reductase inhibitors (statins).

Safety was assessed by the applicant with an integrated summary of safety, information from the Swedish pregnancy registry and the Teratogen Information System, published literature, and a retrospective cohort database study entitled "Study of potential hepatotoxicity of lovastatin in the Northern California Kaiser Permanente liver disease population".

The applicant's Summary of Clinical Safety summarizes the safety information received for prescription lovastatin between 01-Jun-2003 and 31-Dec-2006. This is an update to the Integrated Summary of Safety (ISS) that was submitted with the New Drug Application 21-213 dated August 24, 2004 for MEVACOR™ Daily (lovastatin) Tablets, 20 mg. The ISS dated August 2004 covered the time of first approval in 1987 until 01 June 2003 and utilized data from three sources. The first source was the 2 large, clinical trials mentioned in the efficacy section of this document, EXCEL and AFCAPS/ TexCAPS. The second source was the spontaneously reported post-marketing reports collected in Merck's Worldwide Adverse Experience System (WAES) database which was reviewed through 01-Jun-2003. The third source was published clinical literature as identified through Merck Research Laboratories (MRL) clinical literature database which was reviewed through 31-Mar-2004. The previous ISS also summarized the safety data from the Consumer Use Study of OTC Mevacor (CUSTOM).

There were no Merck sponsored clinical trials with actual usage of lovastatin from 01-Jun-2003 through 31-Dec-2006. In the previous ISS it was estimated that between 1987 and June 2003 there had been over 27 million patient-years of treatment with lovastatin and that, estimated from prescription data, 20 mg daily accounted for approximately 60% of the usage (approximately 17.3 million patient-years of treatment). During the time period of this Summary of Clinical Safety (June 03 to Dec 06) there was an estimated 8.1 million patient-years of exposure to lovastatin, however 40 mg was the most frequently prescribed dosage with over 4 million patient-years of treatment. Lovastatin 20 mg was the second most frequently prescribed dosage with nearly 3 million patient-years of treatment. In total, since the time of first approval until 31-Dec-2006, there has been a total estimated exposure to lovastatin of approximately 35 million patient-years.

Mevacor has lost patent exclusivity in the United States (on 15-Dec-2001) and around the world. During the time period of this Summary generic lovastatin comprised the bulk of lovastatin use. In the United States, Mevacor accounted for less than 1 % (0.9%) of the lovastatin used. Merck's post-marketing WAES database only contains those reports that involve Merck's Mevacor® as well as generic lovastatin of unknown origin. If the manufacturer is known to be a company other than Merck, the report is forwarded to that manufacturer and is not entered into WAES. Thus,

the overall reporting rate during the period of this Summary was much lower than the previous period (5.1 vs. 44 reports per 100,000 patient-years) and limits the completeness of the data.

7.1 Muscle-related Safety

Muscle toxicity with rare cases of rhabdomyolysis has been reported for all marketed statins. Myopathy, which is defined as CK elevations > 10x ULN with muscle symptoms, is estimated to occur between 0.1 to 0.6% of patients evaluated in clinical trials of statins across all doses studied. The more severe form of muscle toxicity, rhabdomyolysis, occurs less frequently and is estimated to have an incidence of 0.03 to 0.05%.[13] The incidence of myopathy by dose in EXCEL was 0%, 0.1%, and 0.2% in the 20 mg daily, 40 mg daily, and 80 mg daily doses, respectively. No cases of rhabdomyolysis associated with lovastatin occurred in EXCEL while one patient treated with lovastatin 20mg developed rhabdomyolysis in AFCAPS/TexCAPS. This case occurred in a patient who had recently undergone prostate cancer surgery. In this same study, 2 patients randomized to placebo had also developed rhabdomyolysis.[14]

With respect to muscle toxicity, the applicant has presented sufficient data to conclude that the risk of myopathy and rhabdomyolysis with lovastatin 20 mg is low. Drug-drug interactions are a concern as lovastatin drug levels may increase in the presence of potent CYP3A4 inhibitors. Additionally, the potential of consumer upward titration of lovastatin to achieve recommended LDL-C treatment goals should be considered in evaluating the risks of muscle toxicity in the nonprescription setting. The results of the CUSTOM actual use study revealed very few patients taking prohibited medications and the majority of these patients took appropriate action (i.e., discontinued lovastatin) or did not experience symptoms of muscle toxicity. DMEP and the advisory committee in 2005 concluded that the risk of myopathy with lovastatin 20 mg is low and is an appropriate dose for nonprescription use.

Muscle-related reports in the worldwide adverse experience safety (WAES) Database
Previously, the applicant performed a search of its worldwide safety database of postmarketing adverse experience reports from approval (1987) until June 1, 2003. The applicant identified 874 reports containing one or more of the search terms. Based on an estimated worldwide exposure to lovastatin of approximately 27 million patient-treatment years, the applicant calculated a reporting rate of myopathy of approximately 3 per 100,000 patient years. Focusing only on reports of rhabdomyolysis, the applicant identified 334 reports representing a reporting rate of 1.2 per 100,000 patient-treatment years.

For this submission, the WAES database was searched for all marketed or study reports from health care providers received between 01-Jun-2003 and 31-Dec-2006 which included any of the following MedDRA preferred terms: compartment syndrome, muscle disorder, myoglobinuria, myopathy, myositis, or rhabdomyolysis. Seventy-one such reports were identified. There were 39 reports of rhabdomyolysis. Thirteen of these reports included use of one or more concomitant therapies which increase the risk of rhabdomyolysis (Table 7.1.2).

Table 7.1.1 Reports of Rhabdomyolysis With or Without Interacting Medication (01-Jun-2003 through 31-Dec-2006)

	Number of Reports of Rhabdomyolysis					
	10 mg	20 mg	40 mg	80 mg	Unknown	Total
No interacting med	--	4	4†	4‡	14	26
Interacting medication	--	--	6§	4¶	3	13
Gemfibrozil	--	--	5§	4¶	--	9
Clarithromycin	--	--	3	--	1	4
Itraconzole	--	--	--	--	1	1
Telithromycin	--	--	--	--	1	1
TOTAL	--	4	10	8	17	39

†including 1 at 60 mg, ‡ including 2 at 160 mg, § including 1 at 60 mg, ¶ including 1 at 120 mg

There were 32 reports of myopathy. Four of these reports included use of one or more concomitant therapies which increase the risk of myopathy (gemfibrozil, itraconazole, nefazodone).

Based on an estimated worldwide exposure to lovastatin of approximately 35 million patient-treatment years, the applicant calculated a reporting rate of myopathy of approximately 0.4 per 100,000 patient years. Focusing only on reports of rhabdomyolysis, the applicant identified 39 reports representing a reporting rate of 0.48 per 100,000 patient-treatment years. These reporting rates are much lower than the previous report in part because of the generic use of lovastatin.

Published Clinical Literature

The National Lipid Association Statin Safety Task Force published its final conclusions in 2006. These were based on a review and independent research of New Drug Application (NDA) information, U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) data, cohort and clinical trial results, and analysis of administrative claims database information and the assessment of its 4 Expert Panels, which focused on issues of statin safety with regard to liver, muscle, renal and neurologic systems. The salient features of that report for muscle safety were:

- Fluvastatin and pravastatin, perhaps because they are the weakest inhibitors of HMG-CoA reductase, appear to cause the lowest frequency of rhabdomyolysis.
- The use of more hydrophilic statins (i.e., pravastatin and rosuvastatin) does not offer protection from muscle toxicity as symptoms of muscle damage and rhabdomyolysis have been reported with these statins.
- The exact mechanism for muscle injury from statin therapy is not known. However, it appears to be related to the blood concentration of the statin, which is influenced by the drug's PK and its potential for drug interactions, the statin dose, and the patients' myopathic risk factors (e.g., age, renal disease, diabetes), but not by the LDL cholesterol level achieved.[15]

The Merck clinical literature database was searched using the terms 'lovastatin' and 'muscle, adverse effect on' for articles published between 01-Apr-2004 and 31-Dec-2006. Several review articles were identified which discussed statin therapy without regard to any one statin and

lovastatin did not appear to be a significant focus of these reviews. The reviews re-iterated the low rate of myotoxicity events. Ten publications of database reviews were identified. In one article, the FDA's postmarketing database was examined (through 31-July-2001) to determine reporting rates for rhabdomyolysis with statin monotherapy and with statin/ gemfibrozil therapy.[16] Domestic cases of statin- and statin/gemfibrozil-associated rhabdomyolysis were culled from FDA's AERS database and reviewed. Rhabdomyolysis was defined as CK≥10,000 IU/L, myopathic signs and symptoms and a clinical diagnosis of rhabdomyolysis. Reporting rates, consisting of number of reported cases/number of prescriptions for each drug, were then calculated to determine whether the reporting of rhabdomyolysis was commensurate with extent of use of each statin in the population. The reporting rates for all statins, except for cerivastatin (4.29), were similar and lower than 1 per 100,000 prescriptions, varying from a low of close to 0 for fluvastatin, up to 0.18/100,000 prescriptions for lovastatin, with pravastatin (0.02), atorvastatin (0.03) and simvastatin (0.11) in between. For lovastatin there were 2.84 reports for 100,000 prescriptions of lovastatin/ gemfibrozil therapy.

Table 7.1.2 Reporting Rates (per 100,000 Rxs) for US cases of rhabdomyolysis associated with statins: all cases* reported through 7/31/01

Calendar years analyzed	Lovastatin: 1988–July 2001	Pravastatin: 1992–July 2001	Simvastatin: 1992–July 2001	Fluvastatin: 1994–July 2001	Atorvastatin: 1997–July 2001	Cerivastatin: 1998–July 2001
All cases						
Cases	180	19	136	1	51	479
#Rxs (000's)†	99 485	83 673	120 188	38 119	149 706	11 172
Crude reporting rate/ 100 000Rx	0.18	0.02	0.11	0.00	0.03	4.29
Monotherapy						
Cases	120	17	99	1	45	200
Estimated #Rxs (000's)‡	97 336	82 000	118 986	37 791	147 610	11 038
Crude reporting rate/ 100 000Rx	0.12	0.02	0.08	0.00	0.03	1.81
Combination with gemfibrozil§						
Cases	60	2	37	0	6	279
Estimated #Rxs (000's)†	2109	1422	962	316	1198	22
Crude reporting rate/ 100 000Rx	2.84	0.14	3.85	0.00	0.50	1248.66

*Cases identified in the AERS database with a CPK > 10 000 IU/L, signs and symptoms (myalgia, myopathy, gait disturbance) and clinical diagnosis of rhabdomyolysis.
†All dispensed Rxs for all years the drug was marketed between 1988–July 2001 (IMS HEALTH NPA*Plus*™, excluding Long Term Care).
‡Estimate of Rxs for statin therapy, with or without concomitant gemfibrozil therapy, based on percentage of mentions (IMS HEALTH NDTI™) summed across all years of marketing for each drug and applied to Rxs for all years each drug was marketed (IMS HEALTH NPA*Plus*™).
§This analysis does not include concomitant therapy with fenofibrate, which was prevalent in 0–1% of mentions across statins, or clofibrate, which occurred only in 0.04% of lovastatin mentions. Few cases of rhabdomyolysis were reported for any statin + fenofibrate or clofibrate; they are not included in this analysis.

Table 4 from Chang JT, Staffa JA, Parks M, Green L. Rhabdomyolysis with HMG-CoA reductase inhibitors and gemfibrozil combination therapy. Pharmacoepidemiol Drug Saf 2004;13:417-26.

One analysis of a smaller database concluded that the odds ratio for statin-induced myopathy (undefined) was 1.1 (95% CI 0.6-2.2) for simvastatin, 0.9 (95% CI 0.5-1.7) for lovastatin, 0.7 (95% C.I. 0.3-1.4) for pravastatin, 0.9 (95% CI 0.4-2.1) for fluvastatin, and 0.4 (95% CI 0.2-0.9) for atorvastatin.[17] In another analysis of 47,917 patients treated with lipid-lowering drugs, 5 cases of severe myositis occurred during treatment.[18] Average incidence per 10,000 person-years for atorvastatin was 0.95 (95% CI, 0.24-0.97); for simvastatin 0.61 (95% CI, 0.31-0.89); for pravastatin 2.52 (95% CI, 0.69-5.32); and for lovastatin 6.47 (95% CI, 0.78-9.62). The conclusion was that the risk of severe myositis (undefined) was low and similar for atorvastatin,

simvastatin, pravastatin, rosuvastatin and fluvastatin with a slightly increased risk for lovastatin, especially in older patients with nephropathy due to diabetes mellitus.

In summary, the published clinical literature for muscle adverse events with the use of lovastatin from the time period of this Summary of Clinical Safety included a number of meta-analyses and reviews of databases of varying sizes. These different studies all reiterated the low prevalence/ incidence of myopathy (including rhabdomyolysis) with statin use.

Myopathy Risk Conclusion
Based on clinical trial data and different analyses of postmarketing spontaneous adverse event reports, the incidence of myopathy and rhabdomyolysis associated with lovastatin use is a very rare event. Drug-drug interactions with potent CYP 3A4 inhibitors are a concern as lovastatin levels may increase and augment the risk of myopathy. In SELECT, 1.4% (21/1493) of the participants who evaluated for Self-Assessment (SA) and 1.4% (21/1494) of the participants who evaluated for Purchase Decision (PD) in SELECT were taking potentially interacting medication. Nineteen percent (4) of the participants who were taking interacting medication (amiodarone, verapamil, cyclosporine, clarithromycin) responded yes to SA and 14% (3) of the participants who were taking interacting medication (verapamil, clarithromycin, ketoconazole) said yes to PD.

Given the lipid-lowering effects and clinical outcome data for lovastatin, the risk of myopathy/rhabdomyolysis does not appear to outweigh the benefit of lovastatin therapy.

7.2 Hepatic-related Safety

7.2.1 Clinical Trial Database
This section presents a review of the data from: (1) the original NDA prescription submission; and (2) the 2 large placebo-controlled, postmarketing studies (the 5- year, Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS] and the Expanded Clinical Evaluation of Lovastatin [EXCEL] study).

NDA Studies for Prescription Lovastatin
At the time of the NDA for prescription lovastatin, 12 of the 1178 (1%) patients who received lovastatin had therapy discontinued or interrupted because of significant (>3 x ULN) increases of hepatic transaminases. This number had increased to 15 (~1.5%) at the time of the 4-month safety update (867 patients received treatment with lovastatin for up to 16 months during that time). The table below summarizes the cases:

Table 7.2.1.1 Listing of Patients in the Original Prescription NDA Who Discontinued Lovastatin Therapy for Hepatic Transaminase Elevations >3 x ULN through 31 Dec 1986 (Cutoff Date for the 4-Month Safety Report)

Patient ID	Gender/ Age	Lovastatin Dose†	Highest ALT (IU/L)	Rechallenge	Possible Contributing Factors
231	M/35	10 mg b.i.d	181	Negative	Transaminase elevations prior to lovastatin
302	M/62	10 mg b.i.d.	180	Positive	Transaminase elevations prior to lovastatin
430	M/62	20 mg b.i.d.	189	Positive	Considerable alcohol intake
435	M/34	40 mg b.i.d.	307	Positive	Transaminase elevations prior to lovastatin
439	M/52	40 mg b.i.d.	111	Positive	Transaminase elevations prior to lovastatin; considerable alcohol intake
442	M/53	20 mg b.i.d.	510	Positive; Negative	Considerable alcohol intake
445	M/37	40 mg b.i.d.	254	Not done	Considerable alcohol intake
2283	M/45	40 mg q.p.m.	380	Positive	Transaminase elevations prior to lovastatin
2285	M/41	20 mg q.p.m.	137	Negative	None identified
2326	F/47	10 mg b.i.d.	315	Negative	Biopsy showed mild focal hepatitis
2139	M/48	80 mg q.p.m.	176	Not done	None identified
2167	F/49	40 mg b.i.d.	145	Not done	None identified
2202	M/24	40 mg b.i.d.	488	Not done	Transaminase elevations prior to lovastatin
9981	M/4	20 mg b.i.d.	168	Not done	None identified
9998	F/12	40 mg b.i.d.	145	Not done	None identified

†q.p.m. = once daily at the evening meal; b.i.d. = twice daily.

Source: NDA 21-213 (Mevacor OTC); Complete Response to Not Approvable Letter, submitted 24-Aug-04, Section F - Integrated Summary of Safety, 2.4.2 Hepatobiliary Adverse Reactions, Table F-14

One patient had a 10 x ULN increase in ALT, but in general, the elevations were 3- to 6- fold. All 15 patients were asymptomatic. Bilirubin and alkaline phosphatase elevations occurred in 6 and 3 patients, respectively; one of the patients had an elevated alkaline phosphatase before lovastatin treatment. Eleven of the 15 patients were taking more than 20 mg of lovastatin per day. Screening tests for hepatitis A and B and cytomegalovirus were uniformly negative. Serology for hepatitis C was not available at that time. The elevations of ALT occurred with a lag time of 3 to 16 months. ALT elevations returned to baseline over several weeks after stopping treatment in all but 2 patients. Nine of the patients were rechallenged: 5 of the rechallenges were positive, 3 were negative, and 1 provided mixed results (i.e., positive with one rechallenge and negative with another). Possible contributing factors to the elevated ALT levels were found in 8 of the patients. Five of the patients had preexisting ALT elevations, and 4 had self-reported heavy alcohol intake. One of the patients who had a negative rechallenge had “mild focal hepatitis” on a liver biopsy. In the five patients with prior elevations of ALT, two had positive rechallenges.

Postapproval Clinical Studies

Two large studies involving almost 15,000 patients were conducted with lovastatin. The first of these studies, EXCEL, was a multicenter, double-blind, diet- and placebo-controlled study in 8245 patients with hypercholesterolemia. The second study, AFCAPS/TexCAPS, was a double-blind randomized placebo-controlled primary prevention study involving 6605 people.

EXCEL

No patient in the study experienced hepatitis. The table below displays the number of patients with consecutive elevations >3 x ULN in hepatic transaminases by dose. The incidence rates in the placebo and 20-mg groups were identical. The incidence rates at the 40- and 80-mg doses suggested a dose-dependent effect.

Table 7.2.1.2 Number of Patients with Consecutive Elevations >3 x ULN in Hepatic Transaminases During the Initial 48 Weeks of Treatment in EXCEL by Dose

	Lovastatin 20 mg Once Daily (N=1642) n (%)	Lovastatin 40 mg Once Daily (N=1645) n (%)	Lovastatin 20 mg Twice Daily (N=1646) n (%)	Lovastatin 40 mg Twice Daily (N=1649) n (%)	Placebo (N=1663) n (%)
Patients with consecutive elevations in ALT or AST	2 (0.1)	12 (0.9)	11 (0.9)	20 (1.5)	2 (0.1)

ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Source: NDA 21-213 (Mevacor OTC); Complete Response to Not Approvable Letter, submitted 24-Aug-04, Section F - Integrated Summary of Safety, 2.4.2 Hepatobiliary Adverse Reactions, Table F-15

AFCAPS/TexCAPS

No adverse experiences of drug-induced hepatitis occurred during the study in the lovastatin treatment group. The table below presents the number of participants with one or more, and consecutive elevations greater than 3 x ULN in ALT alone, AST alone, and ALT or AST. The ALT or AST elevations include increases in ALT alone, AST alone, and both ALT and AST. The category of "one or more elevations" includes participants with (1) single, (2) nonconsecutive multiple, and (3) consecutive elevations greater than 3 times ULN. "Consecutive elevations" includes only those participants with at least 2 consecutive elevations greater than 3 x ULN. Elevated hepatic transaminases resulted in the discontinuation of only 6 (0.2%) participants in the lovastatin group and 4 (0.1%) in the placebo group.

Table 7.2.1.3 Number of Participants With One or More and Consecutive Elevations >3 Times ULN in Hepatic Transaminases in AFCAPS/TexCAPS

	One or More Elevations			Consecutive Elevations		
	Lovastatin (N=3242) n (%)	Placebo (N=3248) n (%)	p-Value	Lovastatin (N=3242) n (%)	Placebo (N=3248) n (%)	p-Value
ALT	55 (1.70)	38 (1.17)	0.077	17 (0.52)	11 (0.34)	0.263
AST	33 (1.02)	26 (0.80)	0.364	5 (0.15)	4 (0.12)	0.754
ALT or AST	66 (2.04)	44 (1.35)	0.035	18 (0.56)	11 (0.34)	0.199

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal

Source: NDA 21-213 (Mevacor OTC); Complete Response to Not Approvable Letter, submitted 24-Aug-04, Section F - Integrated Summary of Safety, 2.4.2 Hepatobiliary Adverse Reactions, Table F-16

There were 18 participants treated with lovastatin (11/1585 [0.7%] receiving 20 mg and 7/1657 [0.4%] receiving 40 mg) who experienced consecutive transaminase elevations >3 x ULN. Fourteen of the 18 lovastatin patients with the consecutive elevations recovered on treatment or had a negative rechallenge. There was no evidence of hepatotoxicity in any of these patients with only 6 (0.2%) participants in the lovastatin group (n=3,304) and 4 (0.1%) in the placebo group (n=3,301) discontinuing from the study due to elevated transaminases.

In AFCAPS/TexCAPS, there were only 4 lovastatin patients who had liver chemistry elevations meeting the criteria for "Hy's Law" (elevated ALT or AST greater than 3 x ULN with concurrently elevated total bilirubin greater than 2 x ULN). The concurrent elevations in total bilirubin and LFTs experienced by these four patients were all single occurrences. In 3 of the 4 patients (0296, 2001, 5421), the elevations resolved at follow up testing. One patient (7923) discontinued and was not retested. Notably, all 4 patients had a concurrent elevation in alkaline phosphatase (ranging from ~1.1 to 3 x ULN); these cases are not technically consistent with "Hy's Law" which excludes events with clinically significant increases in alkaline phosphatase since this may signify biliary obstruction as opposed to hepatocellular injury. As noted in Table 7.2.1.4, three of the lovastatin-treated patients were diagnosed with cholelithiasis and the other with obstructive jaundice. In the placebo group, 5 patients (1540, 2424, 2959, 4870, 5243) had elevated LFTs greater than 3 x ULN concurrently with total bilirubin greater than 2 x ULN. One patient (2959) had chronic active hepatitis, one patient (5243) had hepatitis A, two (1540, 2424) had cholecystitis, and one had colorectal cancer metastatic to the liver (4870).

Table 7.2.1.4 AFCAPS/TexCAPS Summary of Participants Who Experienced Elevation >3 x ULN in AST or ALT (AST >111 IU/L or ALT >120 IU/L) With Concurrent Elevation >2 x ULN in Total Bilirubin (>2.0 mg/dL)

Patient Number	Dose (mg)	Onset: Study Day	AST (IU/L)	ALT (IU/L)	Total (Indirect) Bilirubin (mg/dL)	Alk. Phos. (IU/L)	Comments
Active							
0296	20	1954	635	518	2.3 (0.8)	283	Concurrent elevation in alk. phos. (~2 x ULN); cholelithiasis diagnosed 10 months later. Liver enzymes returned to normal following interruption of drug. Lovastatin resumed without further LFT abnormality.
2001	20	1742	422	525	3.0 (2.2)	159	Slightly elevated alk. phos. (~1.1 x ULN) concurrently. Cholelithiasis diagnosed 5 days later (Study Day 1747). Cholecystectomy ~2 months later. Liver enzymes returned to normal while on lovastatin.
5421	40	298	431	1213	5.9 (1.9)	287	Concurrent elevation in alkaline phosphatase (~2 x ULN); severe cholelithiasis diagnosed the same day (Study Day 298). Liver enzymes returned to normal following interruption of drug.
7923	20	43	112	163	4.7 (2.0)	507	Obstructive jaundice on Study Day 29. Concurrent elevation in alkaline phosphatase (~3 x ULN). Pt. discontinued.

Patient Number	Dose (mg)	Onset: Study Day	AST (IU/L)	ALT (IU/L)	Total (Indirect) Bilirubin (mg/dL)	Alk. Phos. (IU/L)	Comments
Placebo							
1540	N/A	715	131	384	2.9 (2.0)	354	Cholelithiasis diagnosed Study Day 711; concurrent elevation in alkaline phosphatase (~2.4 x ULN).
2424	N/A	1723	327	325	3.2 (0.9)	130	Cholelithiasis on Study Day 1751. Liver enzymes returned to normal.
2959	N/A	317	350	456	2.4 (1.4)	169	Slightly elevated alk. phos. (~1.2 x ULN) concurrently. Discontinued due to chronic active hepatitis; duration 431 days; alk phos and bilirubin still elevated at last measurement and AST/ALT <2 x ULN (Day 557).
		394	218	228	2.2 (1.4)	171	
4870	N/A	1338	294	126	6.7 (2.7)	971	Pt. diagnosed with metastatic liver cancer (primary colorectal).
5243	N/A	1702	1508	2010	8.8 (3.6)	202	Pt. diagnosed with hepatitis A (Day 1695) and discontinued.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal; AFCAPS/TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study ULN: ALT = 40 IU/L; AST = 37 IU/L; total bilirubin = 1.0 mg/dL; alkaline phosphatase = 137 (males 39-48 yrs.), 146 (males ≥49 yrs.), 148 (females 49-68 yrs.), 162 (females ≥69 yrs.)

Source: NDA 21-213 (Mevacor OTC); Complete Response to Not Approvable Letter, submitted 24-Aug-04, Section F - Integrated Summary of Safety, 2.4.2 Hepatobiliary Adverse Reactions, Table F-22

Merck was asked if any of the subjects in EXCEL, the original NDA for prescription Mevacor, or any other clinical trial with lovastatin ≥ two weeks in duration have shown ALT or AST ≥ 3 x ULN with concurrently elevated total bilirubin ≥ 2 x ULN. Additionally, Merck was asked if there were any cases of hepatic failure, hepatic necrosis or hepatitis in any lovastatin clinical trial ≥ two weeks duration. Merck responded that the information being requested is very old clinical data from the early development days of Mevacor. Over the years the clinical trials database at Merck has changed several times, and each time the old database is retired and archived. The Mevacor clinical study data crosses over several databases, and Merck is no longer in a position to access the old data in a meaningful way nor do they have personnel available to support the programming needs required to pull out specific parameters. Any information that Merck currently provides in the OTC applications referring to previously-completed clinical studies on Mevacor Rx has been taken from study reports or publications, and not directly from a database.[19]

In summary, data from large, long-term, placebo-controlled clinical trials and worldwide postmarketing safety reports supported a conclusion by DMEP and the Advisory Committee in 2005 that lovastatin 20 mg has little to no hepatic risk in patients with normal liver tests at baseline. However, the hepatic risks, if any, of statin therapy in patients with liver disease had not been sufficiently studied, particularly since much early liver disease is asymptomatic. The remaining concern was if LFT monitoring would be necessary in consumers with baseline LFT abnormalities to ensure the safe use of this product in the non-prescription setting. The applicant has submitted the findings from three studies to address this deficiency.

7.2.2 Studies in Subjects with Baseline AST/ALT Abnormalities

Study 1[20]*

* The applicant provided financial support to Kaiser Permanente Northern California (KPNC) for the conduct of this retrospective study. Personnel at KPNC performed the chart review and data analysis and prepared the final report. Abstracts and publications of this study are co-authored by KPNC and Merck. This paper has been submitted to a peer review journal and is currently under final review. To date, the study results have been published in abstract form only with poster presentations conducted at the respective professional organizations 2006 annual meetings (DDW, ACG, AHA):

The potential for lovastatin-induced hepatotoxicity in patients with pre-existing liver disease was studied in this retrospective cohort study of adult members of Kaiser Permanente, Northern California (KPNC) Medical Care Program. Eligible subjects had evidence of liver disease at baseline including at least two elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) tests 6 to 18 months apart or carried a liver disease diagnosis (including chronic viral hepatitis B or C without liver failure, other chronic hepatitis, alcoholic liver disease, and metabolic diseases such as hemachromatosis). Eligible subjects had at least 13 months of continuous health-plan membership and were excluded if they had a history of drug-induced liver disease, benign disorder of bilirubin excretion or cancer diagnosis in the prior 5 years; exposure to any statin in the year prior or if they met any laboratory endpoint within the year prior to potential study entry. After excluding the ineligible members, a total of 13,491 lovastatin-exposed subjects and 79,615 non-lovastatin-exposed subjects remained in the final cohort for analysis. Table 7.2.2.1 summarizes the baseline characteristics of the study sample.

Table 7.2.2.1 Baseline Characteristics of Study Sample[20]

	All Patients	Ever Lovastatin Exposed	Never Lovastatin Exposed	*p*-value
Number	93,106	13,491 (14.5%)	79,615 (85.5%)	----------
Age, years [mean (SD)]	48.4 (13.5)	53.9 (11.4)	47.5 (13.6)	<0.0001
Men [N (%]	56,900 (61.1%)	8,394 (62.2%)	48,506 (60.9%)	0.004
Baseline DxCG Score [median (interquartile range)], N=59053	1.23 (0.67 - 2.12)	1.66 (1.05 - 2.71)	1.16 (0.64 - 2.03)	<0.0001
Length of follow-up time, months [median (interquartile range)]	28.8 (12.1 - 58.2)	35.0 (16.0 - 62.0)	27.9 (11.5 - 57.4)	<0.0001
Length of lovastatin exposure, months [median (interquartile range)]	----------	9.1 (4.3 - 19.1)	----------	----------

Note: DxCG score (a generic health-status measurement instrument) is available only for a subset of the full study sample

The predictor variable, exposure to lovastatin, was defined as receipt of a lovastatin prescription as documented in the KPNC automated pharmacy database. Exposure to lovastatin was defined dynamically so that a single subject could contribute both exposed and unexposed time during the follow-up period. To allow for the possibility of persistent hepatic risk beyond the actual exposure period, the authors added an additional 30 days of exposure time to the last prescription. The median length of lovastatin exposure was 9 months. The primary outcome variable was Hy's rule (concurrent serum ALT ≥ 3x ULN, total bilirubin ≥ 2x ULN, and alkaline phosphatase (AP) < 1.5x ULN). There were 2 secondary outcome variables: "liver injury" defined as an ALT elevation between 3 and 10x ULN (moderate) or severe (ALT >10x ULN);

- Avins AL, Manos MM, Levin TR, Ackerson LM, Zhao WK, Murphy RC, Watson DJ, Hwang PMT, Replogle AR, Levine JG. Lovastatin is not hepatotoxic to patients with pre-existing liver disease. (abstract) Gastroenterology 2006:130(4) Suppl 2: A-595.
- Levin T, Avins AL, Manos MM, Ackerson LM, Zhao WK, Murphy RC, Watson DJ, Hwang, PMT, Replogle AR, Levine JG. Hepatic effects of lovastatin exposure in patients with differing types of liver disease. (abstract) Am J Gastroenterology 2006:101 (9): S411.
- Avins AL, Manos MM, Levin TR, Ackerson L, Zhao W, Murphy R. Watson D, Hwang PMT, Replogle A, and Levine JG. Higher dose exposure of lovastatin is not associated with adverse hepatic outcomes in patients with existing liver disease. (abstract) Circulation 2006: 114 (18 Suppl): 4163.

and "cirrhosis/ liver failure" defined as occurrence of a new diagnosis of cirrhosis or a diagnosis that indicated impaired hepatic synthetic function, elevated portal pressures, or liver failure.

Because of the observational nature of this study, there was the potential for observed associations to be partly explained by the presence of confounding variables. The authors identified 4 potential confounders to better assess the causality of an observed association between lovastatin exposure and each of the outcomes. These variables were age, gender, general health status (using the DxCG score, a generic health-status measurement instrument), and concomitant medications (specifically fibrates, itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, all HIV protease inhibitors, and nefazodone).

As shown in Table 7.2.2.2, in the univariate analysis, lovastatin-exposed subjects were significantly less likely to experience either a Hy's rule outcome (incidence rate ratio (IRR)=0.28, 95% CI:0.12 to 0.55), a laboratory-based liver injury diagnosis (IRR=0.50, 95% CI: 0.43 to 0.58), the development of cirrhosis (IRR=0.25, 95% CI: 0.18 to 0.34), liver failure (IRR=0.21, 95% CI: 0.13 to 0.31), or any of the secondary outcomes (IRR=0.48, 95% CI: 0.42 to 0.55). Multivariate adjustment for age and gender did not significantly change these conclusions (see Table 7.2.2.3). Overall, there was no evidence that lovastatin use was associated with adverse hepatic outcomes.

Table 7.2.2.2 Potential for Lovastatin Induced Hepatotoxicity in Patients with Pre-Existing Liver Disease: Univariate Results[20]

	Exposed Person-Time			Unexposed Person-Time				
Outcome	Number of Events	Person-Days of Exposure	Incidence Rate	Number of Events	Person-Days of Exposure	Incidence Rate	Incidence Rate Ratio	95% Confid. Interval*
Hy's Rule	8	4720423	1.69	616	100465184	6.13	0.28	0.12 - 0.55
Combined 2^0	201	3823746	52.57	7751	71100756	109.0	0.48	0.42 - 0.55
Individual 2^0								
Liver Injury	177	3929931	45.04	6661	74556876	89.34	0.50	0.43 - 0.58
Cirrhosis	39	4595492	8.49	3173	94110766	33.72	0.25	0.18 - 0.34
Liver Failure	24	4696685	5.11	2402	98270935	24.44	0.21	0.13 - 0.31
*p<0.00001 for all confidence intervals shown.								

2^o=secondary

Table 7.2.2.3 Potential for Lovastatin Induced Hepatotoxicity in Patients with Pre-Existing Liver Disease: Multivariate Results using Extended Cox Models[20]

Outcome	Person-Time Analysis (IRR)	95% CI	Univariate ECM (HR)	95% CI	Multivariate ECM (HR)[1]	95% CI	Multivariate ECM (HR)[2]	95% CI
Hy's Rule	0.28	0.12 - 0.55	0.31	0.16 - 0.63	0.28	0.14 - 0.57	0.26	0.11 - 0.63
Combined 2º Outcomes	0.48	0.42 - 0.55	0.57	0.49 - 0.65	0.54	0.47 - 0.62	0.56	0.46 - 0.67
Individual 2º Outcomes								
Liver Injury	0.50	0.43 - 0.58	0.58	0.50 - 0.67	0.60	0.51 - 0.70	0.62	0.51 - 0.75
Cirrhosis	0.25	0.18 - 0.34	0.32	0.23 - 0.43	0.24	0.17 - 0.33	0.21	0.13 - 0.33
Liver Failure	0.21	0.13 - 0.31	0.26	0.17 - 0.39	0.19	0.12 - 0.28	0.57	0.47 - 0.67

[1]Covariates include age and gender
[2]Covariates include age, gender, and DxCG (subgroup analysis including only those patients with DxCG scores)
2º=secondary; CI=Confidence Interval; ECM=Extended Cox Model; HR=Hazard Ratio; IRR=Incidence Rate Ratio

The data were also analyzed for evidence of a dose response for the secondary outcome measures. This could not be done for the primary outcome measure since there were so few cases of Hy's Rule. "Exposure" was defined in two ways: total cumulative dose of lovastatin and total cumulative days of lovastatin exposure. Table 7.2.2.4 shows the hazard ratios for the outcome relative to the hazard for those patients with no lovastatin exposure (reference group). Quartiles refer to total cumulative dose of lovastatin over each patient's follow-up period. There was an association between higher lovastatin dose and fewer outcome events in the combined secondary outcomes and the lab-based liver-injury outcome, though the relationship was not strictly linear. The outcome of 'liver failure' showed a slight tendency toward a dose response relationship; this was not seen for 'cirrhosis'. The authors note that the very large number of patients renders all hypothesis tests significant and that in this setting only highly statistically significant results should be considered meaningful.

Table 7.2.2.4 Dose Response for Secondary Outcome Measures

	Lovastatin Exposure Level (Hazard Ratios)				
Outcome	None (reference group)	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Combined Secondary Outcomes	1.00	0.81	0.51	0.47	0.44 *
Individual Secondary Outcomes					
Liver Injury	1.00	0.83	0.49	0.46	0.40 *
Cirrhosis	1.00	0.27	0.38	0.31	0.35 **
Liver Failure	1.00	0.32	0.25	0.21	0.25***
* test for trend: p<0.0001; ** test for trend: p=0.01; *** test for trend p=0.003					

Quartiles refer to total cumulative dose of lovastatin over each subject's follow-up period.

When exposure was defined by the total number of days of lovastatin exposure, there was evidence of a dose-response relationship in the combined secondary outcomes and the lab-based liver injury outcome but no such relationship was observed in the 2 individual disease-based outcomes (cirrhosis and liver failure).

Several sensitivity analyses, which are described in further detail below, were performed and none substantially changed the conclusions of this study. Incidence-rate ratios and hazard ratios were similar regardless of the time period over which hepatic effects of lovastatin were assumed

to persist or the time period over which patients with a Hy's rule outcome were excluded at baseline.

A lovastatin-discontinuation substudy was done to examine the rate at which lovastatin was discontinued among hypercholesterolemic (LDL-C>160 mg/dL) subjects according to baseline confidence of liver disease, in order to see if clinicians or patients stopped the use of lovastatin in subjects with higher liver disease risk (see Table 7.2.2.5). While there were some modest difference in the rates at which lovastatin was discontinued among these subgroups, the differences were small and not likely to represent a strong bias in this study.

Table 7.2.2.5 Rates of Lovastatin Discontinuation by Level of Liver Disease Confidence[20]

			Lovastatin Use		
Group	Category	N	Before index date	After index date	% Discontinuation
1	Liver-dz dx & >=2 LT abnl	6391	2746	2399	12.6%
2a	Liver-dz dx only	6963	2654	2181	17.8%
2b(i)	>=2 LT abnl only	33379	21102	16101	23.7%
2b(ii)	>=1 LT abnl only	100496	51079	42216	17.4%
3	No dx or LT abnl	294017	115043	96353	16.2%

% Discontinuation: cumulative incidence of discontinuing receipt of lovastatin after the index date for a liver-disease patient (Groups 1 and 2) or a matched time timepoint for patients without liver disease (group 3)
Index Date: the date patient developed the conditions that led them to be placed in this category
LT abnl: Liver function test abnormality (AST and/or ALT)
Liver-dz dx: Liver disease diagnosis, the diagnosis used to define entry into the analysis cohort

The authors performed a validation study to examine the positive predictive value of the medical chart diagnosis of fatty liver. A total of 1061 charts that contained a diagnosis of fatty liver were identified from the analysis cohort. A validated algorithm for the diagnosis of fatty liver was applied to this sample to estimate the positive predictive value of a chart-based fatty-liver diagnosis. This substudy used electronic medical records, radiology reports, laboratory tests, and pathology reports. Of the 1061 charts reviewed, 11% (113) were deemed as "definitely" meeting criteria for fatty liver and another 80% (851) were found to "probably" carry the diagnosis of fatty liver. 8% (90) had no evidence to support the diagnosis and 1% (7) could not be classified.

In order to assess the accuracy of the clinician-determined diagnosis of cirrhosis and liver-failure endpoints, the authors performed a validation study of the outcome diagnoses. They drew a random sample of 1200 subjects who experienced one of the specified outcome diagnoses and then investigated the positive predictive value of the database diagnosis by examining the electronic databases and medical chart for evidence for or against the diagnosis. Cases with insufficient data were directly reviewed by a study investigator when the paper chart was available. Of the 1200 selected subjects, 813 subjects' charts contained sufficient information to definitely rule-in the specified diagnosis, yielding a positive predictive value of 68%. An additional 3% (34) subjects had "probable" evidence to support the diagnosis.

The authors' validation work shows that the accuracy of physician coding was generally good, but there was a substantial amount of misclassification that could affect the final results. The identification and coding of fatty liver and cirrhosis was somewhat problematic.

A surveillance bias substudy was performed to detect if a laboratory-based hepatic outcome was a function of the intensity of the clinicians' monitoring of their patients. The difference in frequency of liver enzyme testing was estimated between exposed and unexposed periods in the cohort. The authors found an IRR of 1.46 (95% CI: 1.43 to 1.49) for frequency of testing during the exposed periods compared to the unexposed periods. In other words, clinicians tested their patients 46% more frequently when patients were taking lovastatin than when they were not taking lovastatin. While this is reassuring that fewer laboratory-detected events occurred in the lovastatin group even though this group was actually tested 46% more frequently than the untreated group, it also demonstrated that clinicians believed it represented good clinical practice to do so. One should consider that physician-initiated practice as we go forward in this decision to place statins in the nonprescription setting where there is no health care provider to make that assessment.

The validity of this study would be seriously affected if clinicians avoided using statins in patients who had greater evidence of liver disease. This possibility of channeling bias, or confounding by contraindication, was investigated by examining rates of lovastatin prescription across categories defined by increasing confidence of baseline liver disease. A pre-defined substudy within this study sought to assess for any channeling bias. Three cohorts were assembled with elevated LDL-C levels which varied in terms of their hepatic status: Group 1 had both a liver disease diagnosis and at least 2 elevated liver function tests within an 18 month period; Group 2 had either a liver disease diagnosis (Group 2a) or elevated liver function tests (Group 2b) but not both; Group 3 had no evidence of liver disease. Rates of prescriptions for lovastatin were calculated for each group (see Table 7.2.6). The rates were similar across the groups (Group 1: 38%, Group 2a: 31%, Group 2b: 44%, and Group 3: 41%) indicating that clinicians did not consistently avoid the use of lovastatin in patients with more evidence of liver disease.

Table 7.2.2.6 Rates of Lovastatin Prescription by Level of Liver Disease[20]

		Ever Lovastatin Use			Lovastatin Use After I.D.		
Group	Category	>=1 Rx	None	% Use	>=1 Rx	None	% Use
1	Liver-dz dx & >=2 LT abnl	1682	2102	44.5%	1441	2343	38.1%
2a	Liver-dz dx only	1955	2889	40.4%	1519	3325	31.4%
2b(i)	>=2 LT abnl only	12146	6597	64.8%	8351	10392	44.6%
2b(ii)	>=1 LT abnl only	34775	28871	54.6%	27471	36175	43.2%
3	No dx or LT abnl	102652	147965	41.0%	102652	147965	41.0%

% Use: cumulative incidence of receiving a lovastatin prescription at any time during follow-up period
Index Date: the date patient developed the conditions that led them to be placed in this category
LT abnl: Liver function test abnormality (AST and/or ALT)
Liver-dz dx: Liver disease diagnosis, the diagnosis used to define entry into the analysis cohort

A test of significance on the drug interaction term yielded a p-value of 0.14, indicating no significant interaction between lovastatin and the set of medications tested. This analysis was performed only for the combined secondary outcome variable as there were few events (8) in the primary Hy's Rule outcome.

A sensitivity analysis was done to test the sensitivity of the results to the assumption that the risk of lovastatin exposure ends 30 days after the drug is discontinued. The data were re-analyzed after changing the assumption of potential risk persistence from 30 days after the last dose of lovastatin to permanent risk. For the Hy's Rule outcome and the composite secondary outcome variable, the results were comparable for the two approaches. There were more total events with the infinite-tail approach and a shift in distribution of events from unexposed to exposed periods, but this did not change the overall conclusions of the analyses.

Limitations of this retrospective cohort study:

1. Retrospective studies are subject to "confounding by contraindication" and the physicians may have chosen not to administer lovastatin to patients who had greater evidence of liver disease. A pre-defined substudy within this study sought to assess for any channeling bias and found it was unlikely to be a significant factor.
2. No confirmation of compliance with medication. The analysis variable was "receipt of lovastatin medication" which is a proxy for ingestion of the drug. There is no information regarding the actual adherence to the prescribed medication and these analyses assume that all medication was taken as prescribed. The authors did use the actual number of lovastatin pills obtained by the patient, not just those prescribed by the physician. The study would have been strengthened if LDL-C levels had been monitored as a proxy to assessing for compliance with lovastatin.
3. The author's validation work showed that the accuracy of physician coding was generally good, however there was a substantial amount of misclassification that could affect the final results. The identification and coding of fatty liver and cirrhosis, in particular, seemed problematic.
4. Healthy complier effect: Several studies have shown that patients who adhere well to medications tend to have better clinical outcomes, even if that medication is an inactive placebo[21,22,23,24]. As the authors point out, the possibility that a "healthy complier effect" could be real and operating in this study should be carefully noted. Only an experimental study with random allocation can confidently exclude this possibility.
5. Length of follow-up: This study observed a large number of subjects for several years (median: 29 months). However, we do not know the effects of lovastatin in patients with liver disease over a much longer period which would likely be the common time frame for statin therapy.

Dr. Shewit Bezabeh, an epidemiologist in the Division of Drug Risk Evaluation, was asked by this reviewer to comment on any epidemiologic methodology issues of concern in this study[25]. He had the following concerns:

1. In the study's inclusion criteria, the investigators included multiple potentially disparate clinical entities as evidence of baseline liver disease or evidence of hepatic dysfunction [chronic viral hepatitis (without liver failure), metabolic disorders (Wilson's disease , hemochromatosis), other chronic liver diseases (chronic liver disease and cirrhosis, alcoholic fatty liver, alcoholic cirrhosis of liver, alcoholic liver damage, chronic hepatitis, biliary cirrhosis, Alpha-1 antitrypsin deficiency and other chronic nonalcoholic liver disease)]. This results in substantial clinical heterogeneity amongst these individuals and represents a significant limitation to the study. The study would be substantially more

robust with application of a more specific diagnosis of baseline liver injury OR stratification of the present cohort.

2. In the study's exclusion criteria, some patients with drug induced liver disease and a benign disorder of bilirubin excretion were excluded, limiting the evaluation of drug effects in this subset of the population.
3. In the Lovastatin-Discontinuation substudy, which attempted to assess the potential bias of clinicians discontinuing lovastatin use in patients with baseline liver disease, the analysis showed that there were some differences in the rate at which lovastatin was discontinued among these subgroups. Those with the most "convincing" evidence of baseline liver disease showed the lowest rate of discontinuation (12.6%) and the highest discontinuation rate was observed among patients with persistently elevated LTs (AST/ALT). The reason could be that LT abnormalities are easily detected during visits as opposed to other liver disease categories. In addition, the sub-groups as defined by the investigators may lack clear and meaningful clinical significance. However, the overall discontinuation rate for all exposed groups with liver disease appears significantly higher in comparison to those exposed to lovastatin but apparently free of liver disease or LT abnormalities.
4. Only 2,746 (43%) of the 6,391 hypercholesterolemic members with both a liver-disease diagnosis and persistent LT elevations were taking lovastatin. The fact that 57% of hypercholesterolemic patients with liver disease were not on lovastatin therapy is suggestive of channeling bias (or bias by diagnosis). The finding is supported by increased laboratory monitoring of liver enzymes in the patients with liver disease compared to patients with no disease.
5. The analysis defined lovastatin as dichotomous exposure (as either present or absent) without taking dose, cumulative dose, or cumulative exposure into consideration. This may result in the study's limitation to predict outcome of longer continuous lovastatin exposure in patients with liver disease.
6. Very few Hy's Rule (n=8) events were found during the lovastatin exposure period. The result of this rare primary outcome may have created a problem to use a regression modeling which assumes large sample sizes. In addition, the study was designed to estimate incidence rates and excluded prevalent cases. By excluding pre-existing Hy's rule cases, the effect on lovastatin on pre-existing cases may be underestimated.
7. Surveillance or detection bias (patients with liver disease may be more likely to be monitored) was found; more liver enzyme testing among lovastatin treated patients resulting in differential monitoring.
8. The limitation with identification and coding of fatty liver and cirrhosis may affect the outcome of results.
9. The potential of health modifier effect (subjects who adhere to treatment have better outcomes) can not be properly evaluated in the study.
10. The current study assumes that "lovastatin prescription" as being the same as "medication consumption" without any consideration for "medication adherence". This assumption can introduce bias with regard to medication compliance and exposure to lovastatin. For example, subjects with liver toxicity experiencing the usual symptoms of nausea and vomiting may be reluctant to continue oral medications for a period of time, hence limiting drug exposure. Additional outcome data of lovastatin prescription with cholesterol reduction would have been helpful in support of medication adherence.

Dr. Bezabeh concluded that, although the results of the study (within the limitation of observational study) are consistent with the results of other published studies, a pooled analysis of clinical trials, post marketing studies and opinion of clinicians, by itself, this study does not definitively show that the risk of serious liver injury as defined by the investigators, in lovastatin exposed patients with some baseline liver disease, is not greater when compared to those not exposed to lovastatin.

Study 2[26]

This retrospective study, conducted by investigators at the Indiana University School of Medicine, evaluated 3 cohorts to determine the safety of lovastatin in patients with elevated transaminase levels. Cohort 1 (n=135) consisted of hyperlipidemia patients with elevated baseline liver enzymes who were prescribed lovastatin. Cohort 2 (n=620) consisted of hyperlipidemic patients with normal baseline enzymes who were prescribed lovastatin. Cohort 3 (n=2644) consisted of patients with elevated liver enzymes who were not prescribed lovastatin but had follow-up ALT and/or AST. The mean duration and dose of lovastatin was similar between cohorts 1 and 2 (396 vs. 472 days, and 23 vs. 24 mg/day). Patients with evidence of alcohol abuse, Hepatitis B surface antigen and Hepatitis C antibody were excluded. Elevations in liver biochemistries were defined as mild to moderate or severe as follows:

- mild-to-moderate: elevations of AST and/or ALT *up to* 10 x ULN in patients with normal baseline enzymes or *up to* 10-fold elevations from their baseline values of AST and/or ALT in patients with elevated liver enzymes at baseline
- severe: the development of serum bilirubin > 3 mg/dL regardless of baseline transaminase values or elevations of AST and/or ALT *greater than* 10 x ULN in patients with normal baseline enzymes or *greater than* 10-fold elevations from their baseline values of AST and/or ALT in patients with elevate transaminase enzymes at baseline
- Hy's rule: AST or ALT >3 times ULN and bilirubin >2 times ULN

Values in the three cohorts are summarized in the following table:

Table 7.2.2.7. Values in Study Conducted by Vuppalanchi et al.

	Cohort 1 N=135	**Cohort 2 N=620**	**Cohort 3 N=2245**
Baseline LDL-C (mg/dL)	194 ± 84	184 ± 68	130 ± 49
Baseline AST (IU/L)	46 ± 29	27 ± 7	58 ± 40
Baseline ALT (IU/L)	46 ± 36	18 ± 8	56 ± 51
Baseline Bilirubin (mg/dL)	0.5 ± 0.2	0.5 ± 0.2	0.6 ± 0.4
Follow-up AST (IU/L)	39 ± 18	30 ± 12	64 ± 72
Follow-up ALT (IU/L)	37 ± 27	25 ± 2	86 ± 111
Follow-up Bilirubin (mg/dL)	0.5 ± 0.23	0.5 ± 0.2	0.8 ± 1.0

The upper limits of normal for AST and ALT were 40 and 35 IU/L, respectively

The frequency of mild to moderate elevations, severe transaminase elevations and the occurrence of Hy's rule in the 3 cohorts are summarized in the following table:

Table 7.2.2.8. Frequency of Varying Degrees of Elevations in Liver Biochemistries Over a 12-Month Period in 3 Study Cohorts

	Cohort 1 N=135	Cohort 2 N=620	Cohort 3 N=2245	p-Values	
				Cohort 1 vs. Cohort 2	Cohort 1 vs. Cohort 3
mild-to-moderate elevations of AST and/or ALT	6.6%	3.0%	11%	P=0.03	P=0.2
Severe elevations of AST and/or ALT	0%	0.3%	5.5%	P=0.9	P<0.01
Hy's rule*	0%	0%	3.0%		P=0.03

***** Hy's rule: AST or ALT >3 times ULN and bilirubin >2 times ULN
Cohort 1: hyperlipidemia patients with elevated baseline liver enzymes who were prescribed lovastatin
Cohort 2: hyperlipidemic patients with normal baseline enzymes who were prescribed lovastatin.
Cohort 3: patients with elevated liver enzymes who were not prescribed lovastatin but had follow-up ALT and/or AST.

During the 12-month follow-up, compared to Cohort 2, individuals in Cohort 1 had a higher incidence of mild-moderate (6.6% vs. 3% p=0.03) but not severe elevations (0% vs. 0.3%, p=0.9). No one in Cohorts 1 or 2 developed abnormalities consistent with Hy's rule (defined as AST or ALT >3 times ULN and bilirubin >2 times ULN). Compared to Cohort 3, patients in Cohort 1 had fewer mild-moderate elevations but this did not reach statistical significance (6.6% vs. 11%, p=0.2) and significantly fewer severe elevations (0% vs. 5.5%, p<0.01). In Cohort 3, 3.5% of patients had significant elevations consistent with Hy's rule (p<0.01 vs. Cohort 2, and p=0.03 vs. Cohort 1).

The authors stated that this finding might suggest that patients with elevated baseline liver enzymes who received lovastatin were not at a higher risk of hepatotoxicity from lovastatin than patients with normal liver enzymes. While this may be a logical conclusion, patients with certain known liver conditions (alcohol abuse, Hepatitis B and Hepatitis C) were excluded from this study and the results may not be applicable to other liver diseases.

This retrospective study of an electronic medical record system carries several limitations:

1. Cohort 3, which presumably consist of patients with fatty liver disease only (NASH, NAFLD) who were not on statin therapy, had a rate of severe elevations of AST and/or ALT of 55 per 1000 and a rate of Hy's rule of 30 per 1000. Thus, Cohort 3 exhibits an unusually high incidence rate of severe liver enzyme elevations.[27]
2. The cohorts differed significantly in size: Cohort 1=135, Cohort 2=620, and Cohort 3=2245.
3. The baseline ALT and AST was higher in Cohort 3 (ALT: mean 56 IU/L±51, 1.6xULN; AST: 58 IU/L±40, 1.5xULN) than in Cohort 1 (ALT: 46 IU/L ± 36, 1.3xULN; AST: 56±29, 1.4xULN).

4. Relatively few patients developed severe liver injury, limiting the statistical power of conclusions regarding this endpoint.
5. Retrospective studies are subject to "confounding by contraindication" and the physicians may have chosen not to administer lovastatin to some in the control liver disease population because of potentially relevant characteristics of those patients.

Study 3[28]
(Funded by:
- Donald W. Reynolds Cardiovascular Clinical Research Center at Dallas
- National Institutes of Health; Grant Number: T32-DK-07745, P20-RR-20691)

This study from the University of Texas Southwestern Medical Center, evaluated whether statin use was associated with differences in the prevalence of hepatic steatosis and in the prevalence of serum ALT abnormalities, particularly in subjects with hepatic steatosis. The author states that non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease are independently associated[29,30,31]. In this study, the relationship between statin use, hepatic triglyceride content (HTGC), and serum alanine aminotransferase (ALT) levels was examined in 2,264 Dallas Heart Study participants who were using no lipid-lowering agent (n = 2,124) or using only a statin for lipid management (n = 140). However, lovastatin was used by only 1% of subjects in this study. Statin use was not associated with a greater frequency of hepatic steatosis (38% vs. 34%) or elevated serum ALT (15% vs. 13%) by a pair-matched analysis. Statin use was also not associated with a greater prevalence of elevated serum ALT among subjects with hepatic steatosis (n = 638). This finding persisted when controlling for possible sample bias as a result of current prescribing practices for statins. Among subjects with serum lipid abnormalities who were not using a statin, hepatic steatosis was present in 60% of those with mixed hyperlipidemia and 83% of those with both mixed hyperlipidemia and an elevated serum ALT. The author concluded that statin use was not associated with a higher frequency of hepatic steatosis or serum ALT abnormalities, even among those with hepatic steatosis. Individuals meeting criteria for statin therapy are likely to have coexistent hepatic steatosis.

Limitations of this cross-sectional study for this application include:
1. Only 1% (1 or 2 patients) were taking lovastatin, [(simvastatin (48%), atorvastatin (32%), pravastatin (12%), fluvastatin (6%), cerivastatin (1%)]
2. The analysis relied on a questionnaire to determine statin use by study subjects. The author was dependent on truthful responses by subjects and could not make a determination as to whether subjects were actually prescribed or taking a given medication.
3. Current prescribing practices for statins could have skewed the results of this analysis, as subjects with an elevated ALT at baseline may be less likely to be prescribed a statin. An attempt was made to control for this possibility but sample bias could still exist.
4. Antecedent-consequence certainty cannot be assigned to these findings because of the study's cross-sectional design.

<u>Pravachol Study in Patients with Hepatic Impairment</u>
In NDA supplement 19-898/S-06, Bristol Myers Squibb presented data from a 36-week placebo-controlled trial (CV123246) of pravastatin 80 mg in 326 hypercholesterolemic patients with

chronic, well-compensated liver disease (predominantly NASH/NAFLD and chronic Hepatitis C), to support a proposed labeling revision indicating that LFT's do not need to be performed prior to initiation of therapy or elevation of the dose, but only when clinically indicated.

This submission was reviewed by Dr. Amy Egan, Medical Reviewer for DMEP[32]. In Dr Egan's thorough review, she notes that Study CV123246 was powered for efficacy and not for safety, despite the fact that the applicant's intent was to be able to make safety claims in the label. Therefore, the conclusions that the applicant draws from this study must be viewed with caution. The data presented by the applicant suggest that baseline liver function test abnormalities do not predict patients who are at risk for subsequent worsening in their LFTs or who are at risk for subsequent hepatic injury/failure. The pre-specified protocol endpoint (defined as at least 1 ALT value 2xULN for subjects with normal ALT values at baseline or a doubling of the baseline ALT value for subjects who had elevated [>ULN] ALT values at baseline) was met in 7.5% of pravastatin treated patients and in 12.5% of placebo treated patients. Furthermore, no subject in either group met a protocol endpoint coincident with total bilirubin ≥ 2xULN.

The data do not suggest an increased risk of serious hepatic events in this population of patients with well-compensated liver disease treated with the 80 mg dose of pravastatin. While these data add to the database supporting the safety of the 80 mg dose, and lend support to other small studies demonstrating safety of statins in patients with chronic liver disease, there were some notable deficiencies in the study that prevent one from definitively precluding the need for baseline LFTs with pravastatin 80 mg. Specifically, the trial focused almost exclusively on 2 disease groups – nonalcoholic steatohepatitis/nonalcoholic fatty liver disease (NASH/NAFLD) and chronic Hepatitis C – and in many cases these diagnoses were not supported by liver biopsy. Secondly, the number of patients enrolled in the trial who had elevated baseline LFTs, specifically those who had baseline LFTs greater than 3xULN was small (7 pravastatin-treated patients in the NASH/NAFLD group and 2 in the chronic Hepatitis C group). Third, the number of elderly patients enrolled in the study was small (only 10 patients in the pravastatin group were over the age of 65). And lastly, the number of patients who were regular users of alcohol was small (only 13 subjects in the pravastatin group) which is likely not generalizable to the U.S. population. In this application, the requirement for baseline liver function testing was maintained but the requirement for liver function testing prior to the elevation of the dose was removed.

7.2.3 Hepatic-related reports in the worldwide adverse experience safety (WAES) Database and AERS

In the August 2004 submission, the applicant had reviewed the database for selected hepatobiliary adverse experience. As of June 1, 2003, there were 25 cases of hepatic failure/hepatic necrosis and 251 reports of "hepatitis" reported for lovastatin. Given an estimated worldwide exposure to lovastatin of approximately 27 million patient-years, the calculated reporting rate of hepatic failure/hepatic necrosis and "hepatitis" was 1.0 and 10.4 reports, respectively, per million patient-years of treatment.

Similarly, the FDA's Office of Drug Safety searched AERS for domestic reports of liver failure associated with statin use. Three preferred terms were used in the search criteria: liver failure, hepatic encephalopathy, and liver transplant. A consult was conducted in March 2001 and updated in November 2004. As of February 25, 2000, there were 14 domestic reports of liver

failure associated with lovastatin use. As of November 5, 2004, there were 20 reports. Reporting rates were calculated for the 4-year period post-approval in the March 2001 consult. As summarized by the FDA epidemiologist, the reporting rate for lovastatin was estimated at 2 cases per-million person-years of exposure which approximates the background rate of idiopathic liver failure of approximately 1 per 1,000,000 person-years.

The WAES database was searched for this submission for all marketed or study reports from health care providers received between 01-Jun-2003 and 31-Dec-2006 which included any of the following MedDRA preferred terms: hepatitis cholestatic; hepatitis; hepatitis toxic; hepatotoxicity; hepatomegaly; jaundice. As discussed earlier, Merck's postmarketing database is limited because most lovastatin prescriptions written during this time period were for generic lovastatin (as opposed to Mevacor®) and the adverse event reports will not be submitted to Merck. There were no reports of liver failure during this time period. There were no fatalities. There were ten reports containing the MedDRA preferred terms of interest. Causality due to lovastatin was assessed as 'possible' in one of the 10 reports although no information was provided on important non-drug causes (such as evaluation for viral hepatitis). One report was assessed with a causality of 'unlikely' and a third report did not meet the definition of liver injury since the lab values provided were within normal limits. The remaining 7 reports were categorized as being 'insufficiently documented' due to the absence of information on time to onset since the initiation of lovastatin.

7.2.4 Published Clinical Literature

Numerous articles have been published in the last several years regarding the utility of monitoring liver function tests as a marker to predict drug-induced hepatotoxicity. A summary of some of the pertinent articles follows.[33]

The National Lipid Association Statin Safety Task Force published its final conclusions in 2006 which focused on issues of statin safety with regard to liver, muscle, renal and neurologic systems. The salient features of that report for hepatic safety were:

- During the routine general evaluation of patients being considered for statin and other lipid-lowering therapy, it is advisable to obtain liver transaminase levels. If these tests are found to be abnormal, further investigation should be performed to determine the etiology of the abnormal test results.
- Routine monitoring of liver function tests is not supported by the available evidence and the current recommendation for monitoring needs to be reconsidered by the FDA.
- Patients with chronic liver disease, nonalcoholic fatty liver disease, or nonalcoholic steatohepatitis may safely receive statin therapy.[34]

The Liver Expert Panel which provided advice to the National Lipid Association's Safety Task Force was composed of academic hepatologists with clinical and research interests in nonalcoholic fatty liver disease, lipid metabolic disorders, and drug hepatotoxicity. Additional conclusions of that group include:

- Very rare case reports of liver failure have occurred in patients receiving statin therapy. Because the association between statin therapy and liver failure is rare, it is impossible to directly attribute liver failure to statin usage.

- Liver enzymes and liver function tests need not be monitored in patients receiving long-term statin therapy.
- Chronic liver disease is not a contraindication for statin therapy; compensated cirrhosis is not a contraindication for statin therapy; decompensated cirrhosis or acute liver failure are contraindications for statin therapy; mild-to-moderate alcohol consumption (i.e., up to 1-2 drinks per day) is not a contraindication for statin therapy.[35]

The applicant's clinical literature database was searched using the terms 'lovastatin' and 'liver, adverse effects on', and 'lovastatin' and 'liver enzymes, effect on' for articles published between 01-Apr-2004 and 31-Dec-2006. Six review articles were identified, 5 of these articles were general review articles for which lovastatin was not a significant focus and which, when discussing safety, tended to focus on the muscle side effects. The estimates of the risk of fulminant liver failure attributable to statins ranged from 1 to 9 cases per 1 million patients and these estimates showed little or no greater risk of liver failure than in the general population [36,37,38]. Deaths due to serious liver injury that could be attributed to lovastatin therapy (based on reports in the World Health Organization database) was estimated to be 0.04 per million prescriptions.[29]

Two articles addressed the use of statins in patients with chronic liver disease and concluded that there was little evidence to suggest that the risk of drug-induced liver injury from statins is increased in these patients[29,39]. However, it is worth noting that in the article by Vasudevan and colleagues that in patients beginning statin therapy with baseline elevations in ALT or AST (including patients with chronic liver disease), measurement of baseline liver function, renal function, electrolyte levels, and thyroid-stimulating hormone levels before starting statin therapy is recommended. Furthermore, the physician should consider if the patient has nonalcoholic fatty liver disease and pursue evaluation to establish the diagnosis if necessary; this is not a contraindication for statin therapy if ALT or AST is < three times the upper limit of normal. After starting therapy, monitor ALT and AST at 6 and 12 weeks, and after each dose increase. Likewise in the article by Drs Russo and Jacobson, they recommend that "statins can and should be prescribed for the same indications in people with chronic liver disease as they are in people without chronic liver disease—provided we closely monitor aminotransferase levels for signs of liver toxicity or muscle damage." The authors provide a general guideline of the frequency in which they monitor liver enzymes, based on indirect evidence and on their own clinical experience.

Another publication used an administrative claims database to evaluate the incidence rates of hospitalizations for hepatic medical events in patients receiving lipid lowering agents, including statins.[40] In the 4 ½ year period studied there were 26,122 patient-years of therapy with lovastatin with 16 hospitalizations for hepatic adverse events for an incidence rate of 6.13 per 10,000 patient-years. The authors noted no significant difference in incidence rates for hospitalization between any of the lipid lowering agents given as monotherapy. The study concluded that no increase in risk of hospitalizations due to hepatic adverse events was seen with any statin monotherapy.

In summary, review of the published clinical literature during the time period of this Summary of Clinical Safety confirmed that serious liver injury in patients receiving statins, including lovastatin, was rare.

7.2.5 Hepatic Risk Conclusion

In conclusion, transaminase elevations occur with statin therapy; however, large databases from clinical trials and postmarketing use suggest that these increases rarely result in serious liver injury. The information available since the last ISS on the hepatic adverse effects of lovastatin was reviewed and found to support the safety profile previously established for lovastatin 20 mg. The potential for lovastatin-induced hepatotoxicity in patients with pre-existing liver disease was studied in a retrospective cohort study of adult members of Kaiser Permanente, Northern California (KPNC) Medical Care Program. This large data-base study found that exposure to lovastatin in patients with baseline liver disease was not associated with an increased risk of adverse hepatic outcomes.

In SELECT, 3% (39/1495) of participants in the study who evaluated for SA and 3% (39/1494) of participants who evaluated for PD indicated in the Eligibility Assessment that they had liver disease or liver problems. Of these participants with liver disease, 8% (3) responded yes to the SA question and 8% (3) responded yes to the PD question.

7.3 Pregnancy Risk

All statins, including lovastatin, are designated Pregnancy Category X by the FDA. The information available in Merck's WAES database regarding pregnancy outcomes with maternal exposure to simvastatin and/ or lovastatin from the time of their initial approvals through 31-Dec-2002 has been analyzed and published.[41] The authors reviewed the Merck & Co., Inc. pharmacovigilance database for reports of exposure to simvastatin or lovastatin during pregnancy. The reports were classified as prospective (reported prior to pregnancy outcome) or retrospective (reported after pregnancy outcome) and were evaluated for timing of exposure, outcome, congenital anomalies, and other events. Outcome rates were calculated for prospective pregnancies. There were a total of 477 reports of which 386 were prospective reports and 91 were retrospective reports. The prospective reports included 319 reports with simvastatin and 67 reports with lovastatin. Table 7.3.1 shows the reported 225 prospective pregnancy outcomes.

Table 7.3.1 Prospective WAES Reports of Pregnancy with Lovastatin or Simvastatin

Outcome	n	Denominator	Percent of Reports	US background rate (%)
Elective abortion	49	225†	21.7	22
Spontaneous abortion	18	176‡	10.2	10-20
Fetal death	4	158§	2.5	0.7
Live births	154	225†	68.4	62
Congenital anomalies	6	158§	3.8	3.15

† total number of prospective reports with known outcomes; ‡ total number of spontaneous abortions + live births + fetal deaths; § total number of live births + fetal deaths

Note: 225 known outcomes includes 2 reports of twin gestations
All 6 prospectively reported congenital abnormalities involved maternal exposure to simvastatin

Six congenital anomalies were reported: chromosomal translocation, trisomy 18, hypospadias, duodenal atresia, cleft lip, and skin tag. The rate of congenital anomalies (congenital anomalies/live births plus fetal deaths) was 3.8%, which is similar to the background population rate of 3.15%. There were 13 retrospective reports describing a range of congenital anomalies. No specific pattern of anomalies was identified in either the prospective or retrospective reports. Rates for other outcomes were similar to background rates. The authors concluded that although the number of reports was relatively small, there was no evidence of a notable increase in congenital anomalies in women exposed to simvastatin or lovastatin versus the general population.

The Swedish Medical Birth Registry is a large population-based database containing information on the use of pharmaceuticals during pregnancy. It contains information on nearly all pregnancies resulting in deliveries in Sweden since July 1995. Lovastatin has not been marketed in Sweden and consequently, as of Feb-2007, there were no infants exposed to lovastatin in this database.

TERIS is a computerized database designed to assist healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women. TERIS issued a summary for lovastatin in December 2006.[42] The TERIS summary rated the risk of teratogenic effect as Unlikely. The quality and quantity of data on which the risk estimate was based was rated as Limited. The summary noted that 8 cases of malformations had been reported and, although most of these cases are described repeatedly, the reports contained very limited information and the details were often inconsistent between reports. The summary stated that no causal inference could be made on the basis of these observations.

In September, 2004 The Division of Drug Risk Evaluation searched the AERS database for cases associated with statin therapy and exposure during pregnancy.[43] AERS was searched and identified a total of 195 unduplicated cases of *in utero* exposure to statin therapies. The distribution of cases by molecular entity was: 42 for atorvastatin, 2 for fluvastatin, 25 for lovastatin, 22 for pravastatin, 2 for rosuvastatin, and 102 for simvastatin. For inclusion in the case series, a case must report a temporal association between the maternal parent's use of a drug of interest and the diagnosis of pregnancy. The 195 cases were categorized into one of four outcomes. Outcome and respective number of cases is as follows: live births, 60 cases; elective terminations, 60 cases; spontaneous terminations, 59 cases, and unknowns, 16 cases. For all cases, pregnancy occurred after starting a statin drug. This case series for six statins did identify cases of skeletal malformation, but the number of cases was small (11/195). In addition, the rate of occurrence for each reported defect was unknown because the cases were reported spontaneously to AERS. No trend or pattern was found to establish a causal association between the *in utero* statin therapies and the identified birth defects.

Pregnancy Risk Conclusion

All statins are currently labeled Pregnancy Category X which means that human/animal fetal risk outweighs clinical benefit. There have been reports of congenital anomalies with human use although the causal role of lovastatin for these findings is uncertain. While the risk of lovastatin use during pregnancy cannot be ruled out, if a risk does exist it appears to be small.

7.4 Amyotrophic lateral sclerosis

Using spontaneous reported adverse event databases, FDA and others have observed disproportionate reporting rates, or data mining signals, for statins and amyotrophic lateral sclerosis (ALS).[44] Data mining signals are subject to a host of limitations and in isolation they should never be interpreted as indicating a cause-and-effect relationship between a drug and a reported adverse event.

Given the extensive use of statins and the seriousness of ALS, FDA further evaluated the data mining signal by retrospectively analyzing data from a large number of placebo-controlled statin cardiovascular trials. In a dataset that included all marketed statins and comprised approximately 400,000 patient-years of exposure, there were 9 cases of ALS diagnosed in patients randomized to placebo and 9 cases in patients randomized to statin. Therefore, the incidence of ALS was nearly identical (~ 4.4 cases per 100,000 person-years) in statin compared with placebo-treated patients. Although the clinical trials have several shortcomings with respect to assessing the incidence of ALS, the similar rates of this disease in placebo and statin groups is reassuring. It is also reassuring that the incidence of ALS in the U.S. during the past 20 years appears to have been stable, despite a very large increase in the use of statins in older Americans during this same time period.[45]

FDA is aware of an ongoing case-control study examining the question of statin exposure and risk for ALS. Results from this study are expected in mid-to-late 2008.

Additional information on this topic will be presented at the December 13, 2007, Advisory Committee Meeting.

7.5 Neurologic/Psychiatric Adverse Reactions

The applicant's previous ISS reviewed the available information on lovastatin use and peripheral neuropathy or paresthesia. In the 2 year Expanded Clinical Evaluation of Lovastatin (EXCEL) study both peripheral neuropathy and paresthesia were reported with similar frequency in the placebo and lovastatin groups and there was no evidence of a dose-response[46] The reporting rate for reports of peripheral neuropathy in the WAES database was ~1.3 reports per 100,000 patient-years of treatment. This did not exceed the background incidence in the general population for peripheral neuropathy not associated with alcohol use or diabetes (7 to 15 cases per 100,000 patient years).

The applicant's Summary of Clinical Safety for this submission reviews all reports in the neurologic and psychiatric System Organ Classes since the previous ISS. The WAES database was searched for all marketed or study reports from health care providers received between 01-Jun-2003 and 31-Dec-2006 that mapped to the System Organ Classes of 'Nervous system disorders' and 'Psychiatric disorders'. Seventy-three such reports were identified. The reports generally had little detail and often lacked information on outcome. The adverse event terms were generally non-specific and the lack of data precluded further evaluation of them. No pattern of events appeared evident as the reports were scattered across a wide range of terms.

The relevant clinical literature since the previous ISS was reviewed as well. The articles published during the reporting time period addressed a range of neuropsychiatric concerns. Neuropsychiatric events which were addressed in more than one article were cognitive function, stroke, and peripheral neuropathy. Three articles addressed peripheral neuropathy. Two of these were review articles which concluded that a risk of peripheral neuropathy with statin use may exist, but if so, the risk appeared to be minimal.[47,48] The third article was of a database study which identified 272 patients with idiopathic polyneuropathy and 1,360 matched controls.[49] Statin use was prescribed to 8.8% of patients (mean duration of use 18 months) and to 6.9% of controls (mean duration of use 14 months) with similar dose equivalents in both groups. Statin use prior to diagnosis was not significantly greater in patients than in controls (O.R. 1.30, 95% C.I. 0.3 – 2.1).

Overall, it appeared that statin use may or may not prevent the onset of dementia, was beneficial in preventing stroke, and may or may not be associated with a small risk of peripheral neuropathy.

7.6 Zocor HeartPro (simvastatin 10 mg)

Lovastatin is not currently approved as an OTC medication anywhere in the world. Simvastatin 10 mg is approved as a behind-the-counter medication in the United Kingdom with the brand name of Zocor HeartPro. It can be dispensed by a pharmacist without the involvement of a physician and was approved in August-2004. Between August-2004 and 30-Apr-2007 an estimated 9,007,796 tablets have been distributed. This is equivalent to 24,679 patient-years of treatment, assuming a dosing regimen of one tablet daily.

The WAES database was searched by the applicant for all reports (consumer or health care provider) for Zocor HeartPro from the time of its approval through 26-Apr-2007. Twenty-four reports were identified. Gender was provided in 19 reports (13 men and 6 women). Age was provided in 7 reports: 48 years, 53 years, 55 years, approximately 55 years, 56 years, 49 years, and 67 years. Outcome was provided in 11 reports with 9 reports stating that the patient recovered and 2 reports stating that the patient did not recover. In addition, 6 reports stated that there was a positive dechallenge, 1 report included a negative dechallenge, and 1 report included a positive rechallenge. No reports had a fatal outcome. There were 2 serious reports. One concerned a male who developed idiopathic thrombocytopenia purpura after having received simvastatin for an unspecified period of time. The patient was hospitalized 3 times and subsequently "the patient's condition was under control". No laboratory data, information on concomitant medications or conditions, or any actions taken with Zocor HeartPro were provided. The second serious report was from a 59 year old white male who received Zocor HeartPro in the absence of any concomitant therapies. The patient subsequently developed severe diarrhea, drowsiness and headaches. He was treated by his physician with tablets for the diarrhea. Zocor HeartPro was also discontinued, and the patient subsequently recovered.

The published literature was reviewed for information regarding Zocor Heart Pro in the United Kingdom. One editorial in Lancet commented that OTC statins were a bad decision for public health.[50] Reasons included that there are no trials of OTC statins for primary prevention of heart

disease. There were no data on compliance with OTC statins, which for products that need to be taken daily long-term is a concern. The authors question whether those who buy simvastatin will also stop smoking, lose weight, and do more exercise, or will they substitute drug use for lifestyle modification? Will pharmacists have the time to determine the individual's risk of coronary heart disease before selling the drug and also to give lifestyle advice? The editorial comments that, according to an appraisal by the University of British Columbia, if the five major statin primary-prevention trials are combined (and none studied simvastatin), then 71 patients with cardiovascular risk factors have to be treated with a statin for 3–5 years to prevent one heart attack or stroke. Prescribed statins (pravastatin 40 mg, atorvastatin 10 mg, and lovastatin 20–40 mg) have not been shown to provide an overall mortality benefit in primary-prevention trials. The authors argue that it is unlikely that a low dose of OTC simvastatin will do what has not been found in controlled settings. And lastly, pharmacists will need to be vigilant about the potential for interaction with prescribed drugs such as other cholesterol-lowering drugs, anti-coagulants, antifungals, or antibiotics.

Another article evaluated the impact of OTC simvastatin on statin prescriptions in the UK.[51] The United Kingdom (UK) government changed the prescription policy of statins, making low-dose simvastatin (10 mg) available as an over-the-counter (OTC) drug in August 2004. The authors assessed the impact of this policy change on statin prescribing. They examined all statin prescriptions in the General Practice Research Database (GPRD), a well-validated database of approximately 3.5 million patients, from the first quarter of 2001 to the second quarter of 2005. From 2001, the number of statin prescriptions written for GPRD patients was increasing by approximately 437 prescriptions per 100,000 people per quarter until the time of the policy change. Over the four quarters post-policy implementation, however, this trend changed abruptly ($p<0.0001$) with a decrease of 281 prescriptions per 100,000 people per quarter. This decrease was not restricted to prescriptions of 10 mg statins but was also observed for statin prescriptions of ≥20 mg. Several other cardiovascular medications displayed a similar trend as that observed in the number of statin prescriptions. This trend was not observed among non-cardiovascular control medications. The authors suggest that the policy allowing the OTC sale of 10 mg simvastatin has had a significant impact on statin prescriptions by general practitioners and that this new policy may also be leading to less aggressive statin therapy. The authors state that an alternative explanation for the observed decrease in statin prescriptions may be related to the unknown factors responsible for the overall decrease observed with other cardiovascular prescription drugs.

7.7 Self-selection Study (SELECT)

The applicant provided results of two label comprehension studies, The Muscle Warning Comprehension Study (P088) and The Pivotal Label Comprehension study (P087), which will be reviewed by Capt. Laura Shay from ONP/DNCE. Dr. Linda Hu, ONP/DNCE will review the non-drug, self-selection study entitled “Self Evaluation of Lovastatin to Enhance Cholesterol Treatment (SELECT, P086). These studies are reviewed in detail by the Division of Nonprescription Clinical Evaluation, Office of Nonprescription Products and these analyses are included in this briefing document.

Deficiencies in SELECT that impact on the safe and effective use of this product include:

- 13% (29/220) of the women in the LDL-C paradigm who were too young made a positive self-assessment decision
- 29% (29/101) of women with a positive self-assessment decision were too young
- ~11% of men and over 40% of women with a positive self-assessment decision were of low CHD risk (<5% risk of CHD in 10 years)
- 22% (60/268) of the participants who did not know their LDL-C value made a positive self-assessment decision in the LDL-C paradigm
- 43% (52/122) of participants with a self-reported LDL-C higher than 170 mg/dL made a positive self-assessment decision; 17% (26/153) of participants with a self-reported LDL-C lower than 130 mg/dL made a positive self-assessment decision
- On average, about 30% of participants with CHD, diabetes mellitus, or stroke wanted to purchase the product
- Over 30% of participants already taking a lipid-lowering medication made a positive self-assessment decision. Over 50% of those who made a positive purchase decision but were already on lipid-lowing medications stated they would take Mevacor Daily "in place of" their lipid-lowering medication and over 25% would take Mevacor Daily along with their lipid-lowering medication. The 3 most commonly taken lipid-lowering medications used by participants in the LDL-C paradigm were atorvastatin, simvastatin, and rosuvastatin—significantly more potent statins than lovastatin

7.8 Safety Conclusions

Data from controlled clinical trials and post-marketing spontaneous adverse event reporting support the conclusion that risks of muscle and hepatic toxicity are rare events that do not offset the benefits associated with long–term use of lovastatin 20 mg in otherwise healthy individuals. The applicant has provided sufficient evidence that the risk of hepatotoxicity is minimal in patients with common asymptomatic liver diseases to address the safe use of lovastatin 20 mg in the nonprescription setting. Other safety concerns include drug-drug interactions which affect the risk of myopathy and exposure during pregnancy. The applicant proposes to manage these risks through labeling. Areas of concern in the SELECT Study are listed in the previous section, Section 7.7. The self-selection and actual use studies, SELECT and CUSTOM, have not convinced this reviewer that there is adequate consumer comprehension of the proposed product label to ensure safe and effective use of this product.

If Mevacor Daily is approved, this reviewer recommends stronger labeling language regarding consumers already taking a lipid lowering prescription medication and those with a history of CHD, diabetes, or stroke. This reviewer approached this submission primarily using the LDL-C label paradigm. If the applicant proposes that the Total Cholesterol (TC) label paradigm should be the label for MEVACOR™ Daily, they must provide evidence that demonstrates that the eligibility criteria in that label (for both men and women) target the same CHD risk population as the LDL-C paradigm. Also, they must provide evidence that consumers using the TC label can appropriately assess their treatment goal which, as per NCEP ATP III guidelines, is based on an LDL-C target.

8 ADDITIONAL CLINICAL ISSUES

8.1 Literature Review: Pros and Cons of OTC Statins

Relevant portions of the literature review conducted for this application appear in appropriate sections of the review. In addition, this reviewer has included articles that address the pros and cons of over-the-counter statins, in general, below:

Abrams J. Over-the-counter statins: a new controversy. Nat Clin Pract Cardiovasc Med 2005; 2(4):174-5.

> Abrams asks if the benefit is worth the risk and how can OTC statin availability be made as safe as possible. Abrams concludes that it seems reasonable that knowledgeable pharmacy staff, well-educated as to the rationale for OTC statin use, could effectively control drug dispensation in the US, readily screening individuals with a short, on-the-spot questionnaire. As mentioned by the FDA advisory panel in 2005, a change in congressional legislation would probably be required to establish UK pharmacists-based OTC control in the US. Clear guidelines must be established to define the individuals who would benefit from low-dose OTC statins. For people already receiving statins, careful attention must be given to assure that the desired degree of lipid lowering is achieved with low-dose OTC statins. If care and thought are taken in designing an OTC program that is educational and emphasizes the adverse effects and potential drug–drug interactions, with the admonition that concerns should be directed to knowledgeable healthcare professionals, a truly effective consortium consisting of industry, pharmacists and the consumer could be achieved.

Barter PJ, Rye KA. The Argument Against the Appropriateness of Over-the-Counter Statins. *Circulation* 2006; 114:1315-1320.

> This article argues against making statins available OTC on 3 grounds: (1) the risk of adverse effects may no longer be outweighed by the benefits if statins are used in people at low CV risk; (2) high-risk people may not achieve the low LDL targets shown to be desirable to maximize risk reduction; and (3) other lipid abnormalities such as a low high-density lipoprotein (HDL) cholesterol may not be identified or treated.

Brass EP, Allen SE, Melin JM. Potential impact on cardiovascular public health of Over-the counter statin availability. Am J Cardiol 2006; 97:851-6.

> Brass et al write that according to the risk profile of CUSTOM consumers, the use of 20 mg lovastatin for 10 years would be expected to prevent approximately 33,100 CHD events per 1 million users. This represents a 10-year number needed to treat of 30 consumers. On a population basis, OTC statin availability is likely to result in clinically meaningful reductions in CHD morbidity and mortality.

Choudry N, Avorn J. Over-the-counter statins. Ann Intern Med 2005; 142:910-13.

> Although statins have infrequent side effects and have been shown to be effective in moderate-risk primary prevention populations, many questions remain unanswered about their effectiveness at lower doses in over-the-counter use, the ability of patients to self-select themselves for appropriate therapy, and the social and economic implications associated with this method of distribution for preventive medications. A rational policy decision concerning over-the-counter statin use will require an effectiveness trial to provide data on how such drugs would be used in

this context, as well as on the clinical outcomes that could be expected from this novel "route of administration."

Davidoff F. Primary prevention with over-the-counter statins: A cautionary tale. Clin Pharmacol Ther 2005; 78:3:218-20.

In this article, Dr. Davidoff discusses his vote against making a statin (lovastatin) available over-the-counter for primary prevention of CVD at the January 2005 Advisory Committee meeting. He summarizes the clinical concerns noted in Dr. Strom's article and adds in 3 overarching issues that Strom did not discuss—paternalism, informed choice, and cost—all of which argue against approval.

The issue of paternalism can be framed as follows. Why should regulations prevent consumers from freely choosing to assume the risks and costs associated with primary prevention with OTC statins to realize its gains? How can free choice and protection of the public health be balanced in the most responsible way? In making that decision, Davidoff argues that the FDA must recognize that primary prevention carries with it a particular responsibility, that is, the need to be extra careful in minimizing potential harm.

Regarding the issue of informed choice, Davidoff contends that if consumers could be fully informed about the benefits and risks involved, that he would have been much more inclined to vote for approval of OTC statins for primary prevention. Unfortunately, the ability to provide that information using the AFCAPS/TexCAPS study and estimating a number needed to treat to prevent a CV event is highly questionable. Even if solid data on the efficacy of OTC statins in primary prevention were in hand, informing users of those benefits in a way that would allow for truly informed choice would be a formidable challenge. For all other OTC drugs, the regulatory process requires that users should be able to self-diagnose the indications for use with reasonable accuracy. Those indications must, therefore, be concrete and obvious. The benefits are also expected to be correspondingly concrete and obvious, as well as prompt. In contrast, the benefits of primary prevention with OTC statins are delayed, abstract, and subtle. To be properly informed, OTC statin users would, therefore, need to understand that although the benefits may be significant and quantifiable across an entire population the benefits to any single user are uncertain; they are, in fact, "statistical." Moreover, they would need to understand that a variety of factors can affect the degree of benefit and that benefits, when and if they do occur, are manifest only after about 2 years of continuous use. In effect, approving statins for OTC primary prevention would amount to a huge uncontrolled experiment, in which neither the benefit nor the risk side of the equation was known.

Davidoff discusses the issue of cost of primary prevention with OTC statins in relation to its clinical value, noting that the data is lacking to provide a definite answer.

Davidoff concludes with the following questions: "The availability of statins over-the-counter could prevent thousands of cardiovascular events that would otherwise occur"—maybe. "The risks associated with their use are reasonable, relative to their benefits"— possibly. "The information that potential users would need to make informed decisions about use is available"—apparently not. "We have the ability to get people to understand that information adequately"—uncertain. "The associated costs are worth the gains, both on an absolute scale and relative to the costs of other medical interventions"—highly doubtful.

Fuster V. A new perspective on nonprescription statins: An opportunity for patient education and involvement.

Fuster writes that without increased patient education and access to diagnostic and treatment tools, progress on the CHD epidemic will remain stalled. Clear advantages to increased patient participation, education, and responsibility for major public health issues have been proven repeatedly. Nonprescription statins could positively impact efforts toward increased patient education and participation regarding primary prevention of CHD. Consumer-friendly diagnostic and treatment tools regarding lipid management and CHD risk reduction that would accompany nonprescription statins could motivate millions to take actions such as getting a cholesterol test, adopting a healthier lifestyle, and discussing cholesterol management with a health-care professional. To realize this potential, sponsors of nonprescription statin proposals must continue development of improved product labeling and educational messages, and to demonstrate their effectiveness in driving appropriate consumer behavior. The cardiology community should lead a more public discussion of how nonprescription statins could become a component of a primary prevention patient education and participation strategy, and in so doing, take much needed action toward alleviating the CHD epidemic.

Grotto Jr AM. The case for over-the-counter statins. Am J Cardiol 2004; 94:753-6.

Grotto concludes that there is clearly a desire for complementary approaches to lifestyle therapy based on the amount of money spent on vitamin supplements and other OTC products with poor bona fides as preventive medicine. An OTC version of a statin with demonstrated primary-prevention benefits will offer another therapeutic alternative for patients who have intermediate risk and require primary prevention. The decision in the United Kingdom to permit OTC statins makes the debate a timely and important one for the United States.

Gotto Jr AM, Phil D, LaRosa JC. The benefits of statin therapy - what questions remain? Clin Cardiol 2005; 28:499-503.

Gotto A. Over-the-counter statins and cardiovascular disease prevention: Perspectives, challenges, and opportunities. Clin Pharmacol Ther 2005; 78:3:213-17.

There are several potential advantages to being able to obtain a statin without a prescription: improved and broader access, increased education about risk factor modification, greater patient autonomy in making decisions about treatment, and health care savings as a result of reduced coronary events. However, the challenges conferred by nonprescription status are equally great. In its rejection of the lovastatin application, the FDA panel gave 2 compelling reasons for its decision. First, the panel believed that the current drug-delivery infrastructure in the United States was not able to provide the necessary safeguards to support a nonprescription statin. Second, the panel believed that the availability of a nonprescription statin would negatively affect efforts to promote preventative lifestyle measures such as diet and exercise. These and other critical issues must be resolved before OTC statins would make further headway. There is almost no disagreement that statins are cardioprotective drugs with few adverse side effects. Whether statins will ever make the leap from prescription to OTC remains to be seen. Given the continuing epidemic of CHD morbidity and death in the United States, exploration of all options that may help prevent its further spread is a worthwhile endeavor.

Gotto AM, Jr. Over-the-counter statins are worth considering in primary prevention of cardiovascular disease. Circulation 2006; 114:1310-4.

Although there is almost total consensus that statins are cardioprotective drugs with few adverse side effects, obstacles remain for the approval of OTC statins, largely questions related to how

best to implement an OTC program. Whether statins will ever make the leap from prescription to OTC remains to be seen. Nevertheless, the discussion is worthwhile in the face of the continuing epidemic of CHD morbidity and mortality in the United States. At present, proponents require a major feat to break the stalemate over OTC statins in the United States. A change in the law that facilitates behind-the-counter pharmacy services, a more convincing use study that addresses the concerns raised by CUSTOM, or data that demonstrate the public health benefit of OTC statin access could provide that impetus. Discovering whether an OTC statin would be a viable option for patients who need treatment will help shape future efforts in cardiovascular prevention.

McKenney JM, Brown WV, Cohen JD, Cahill E. The national lipid association surveys of consumers, physicians, and pharmacists regarding an over-the-counter statin in the United States: Is this a good idea? Am J Cardiol 2004; 94(9A, Supplement 1):16F-21F.

Surveys commissioned by the National Lipid Association (NLA) were conducted to determine the current attitudes and perceptions of physicians, consumers, and pharmacists regarding the impact of an over-the-counter (OTC) statin. This NLA consumer survey indicates that consumer-respondents are generally enthusiastic about having an OTC statin option. However, the survey also indicates that some currently treated and high-risk patients would also purchase and take this therapy, which raises obvious concerns. Most consumer-respondents (83%) indicated that they would consult their physician or another healthcare professional before purchasing such a drug, and that they would continue to do so while taking the statin.

Physicians are cautious, even reticent, about an OTC statin option, as indicated by the results of their survey. Only about half wanted to learn more about this option, and fewer would support a consumer who is interested in pursuing it. Physician reluctance is likely due to the perception that OTC statin therapy could conflict with the patient's medical care. Physicians may also recognize the complexity of the decisions that need to be made to initiate and successfully carry out OTC statin therapy. In fact, both physicians and pharmacists were concerned that OTC statin therapy would divert patients from more effective prescription therapy; they also expressed concern about side effects, drug interactions, and the patient's ability to self-manage OTC statin therapy.

Although pharmacist-respondents in the NLA survey indicated interest in helping consumers learn about OTC statin therapy, arrange for follow-up lipid testing, and provide monitoring and advice, it must be noted that these services are currently not routinely available from pharmacists.

The NLA believes that the question regarding an OTC statin option is less about the benefit of treatment, because effective CAD risk reduction has already been documented in several large randomized clinical trials, or about safety, because OTC statin therapies have proved safe in many long-term clinical trials involving thousands of person- years. Rather, the key question is how the consumer will be supported to carry out safe, wise, and effective self-care to prevent CAD events.

Somberg J. Should statins go OTC [Editorial]. Am J Ther 2004; 11:1-2.

The author contends that the forces behind OTC statins are misguided at best. The industry is pushing agents going generic for OTC status to give them a new "commercial life" when more effective therapies of this class are available and physicians can use properly selected doses. While some believe the OTC switch will lower costs, this is not what happened with non-sedating antihistamines and the less effective statin therapy will increase morbidity and mortality and thus increase health care costs when all considerations are taken into account.

Strom BL. Statins and over-the-counter availability. N Engl J Med 2005; 352:1403-5.

As summarized in the Davidoff article, Strom articulates at least 11 "core" clinical concerns that led him to conclude the following: "Although statins are great prescription drugs, these considerations suggest that they would make poor over-the-counter drugs." These concerns were as follows. (1) Unlike the indications for virtually all other OTC drugs, the condition being treated is not self-diagnosable. (2) Contrary to the conditions for use of all other OTC drugs, OTC statin therapy is expected to be long term. (3) Efficacy is dose-related and requires monitoring for titration, which is optional for OTC use. (4) The lower dose proposed for OTC availability, primarily to increase the margin of safety, could prevent more appropriate dosing. (5) OTC users might mistakenly conflate more serious disease (e.g., angina) with hypercholesterolemia. (6) People might use the drug simply for "peace of mind" rather than clinical efficacy. (7) The efficacy of statins for a self-diagnosed condition has never been clearly demonstrated. (8) Complications and contraindications of statins (largely liver and muscle damage) are not self-diagnosable. (9) Adherence, which is notoriously poor in long-term prescription drug therapy, is likely to be even worse for an OTC drug (which many people do not consider a "real" drug), particularly because people will be paying for it out of pocket. (10) Users who believe that "more is better" might increase the dose inappropriately, thus worsening the risk-benefit ratio. (11) The safety of statin use in pregnancy has been seriously questioned.

Strom concludes that the motivation for making statins available over the counter is understandable: to increase access to an effective and underused therapy. But it is unclear that such a switch would help to achieve that goal.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	November 1, 2007
To:	Eileen Craig, MD Medical officer Division of Metabolic and Endocrine Products (DMEP)
Thru:	Mark Avigan, MD, C.M, Director Division of Drug Risk Evaluation (DDRE)
From:	Shewit Bezabeh MD, MPH, Epidemiologist
Subject:	Consult Mevacor OTC observational study
Drug Name(s):	Mevacor Daily/ lovastatin 20 mg OTC
Application Type/Number:	NDA 21-213
Submission Number:	
Applicant/sponsor:	Johnson & Johnson / Merck Consumer Pharmaceuticals Co. (JJMCP)
OSE RCM #:	RCM 2007-1700

1.0 INTRODUCTION:

Two review cycles have been completed by the FDA for NDA 21-213 for the proposed prescription-to-OTC switch for lovastatin (Mevacor). During the second review in February 2005, the NDA received a non-approvable letter due to multiple deficiencies. One of the concerns was the lack adequate safety data to evaluate hepatic risk with the use of lovastatin in patients with asymptomatic liver disease. During the Advisory Committee (AC) presentation, the sponsor presented a preliminary data of a pharmacoepidemiologic study of the safety of lovastatin in patients with pre-existing liver disease. After the AC meeting, the sponsor submitted the pharmacoepidemiologic study, "study 4080", and a retrospective cohort database study that was conducted in patients with preexisting liver disease who were treated with lovastatin.

DMEP is now requesting a consult from OSE/DDRE with the following questions:

1. Are there any epidemiologic methodology issues with this study that are of concern?
2. Is the possibility of channeling bias or "confounding by contraindication" adequately addressed by the applicant by their examination of lovastatin prescription rates across categories defined by increasing evidence of hepatic disease (no evidence of liver disease, the presence of a liver-disease diagnosis or abnormal LFTs, or the presence of both a diagnosis and abnormal LFTs)?
3. Are the concerns of differential monitoring of liver function tests and differing rates of statin discontinuation between groups adequately addressed by the applicant?
4. How much of a concern is the misclassification of fatty liver and cirrhosis in the overall conclusion?
5. How much of a concern is the potential for "healthy complier effect" in this study?

2.0 MATERIAL REVIEWED

Study 4080, entitled "Study of potential hepatotoxicity of lovastatin in the northern California Kaiser Permanente Liver disease population" is a retrospective, observational study of lovastatin exposure among Kaiser Permanente of Northern California (KPNC) members with liver disease or evidence of hepatic dysfunction as per the investigators criteria. KPNC is a large integrated health plan with over 3.2 million members and an electronic information system conducive for pharmacoepidemiologic studies.

2.1 Population:

Subjects were adult members of KPNC who had evidence of liver disease at baseline as per the investigators or who were at high risk for the development of liver disease, either because of persistently elevated liver enzymes or a liver-disease diagnosis, including chronic hepatitis B and C infections. Subjects met the following criteria for enrollment:

Inclusion Criteria

- At least 18 years of age
- At least one year of continuous KPNC enrollment after January 1, 1995
- At least 30 days of KPNC membership after enrollment

The presence of at least one of the following

1) Elevated ALT levels on at least two occasions 6 to 18 months apart (starts at the time of the second abnormal ALT)

2) Elevated AST levels on at least two occasions 6 to 18 months apart (starts at the time of the second abnormal AST)

3) Diagnosis of liver disease, defined as one of the following:

- Chronic Viral Hepatitis (without liver failure)
- Metabolic Disorders (Wilson's disease , Hemochromatosis)
- Other Chronic Liver Diseases (Chronic liver disease and cirrhosis, alcoholic fatty liver, alcoholic cirrhosis of liver, alcoholic liver damage,

chronic hepatitis, biliary cirrhosis, Alpha-1 antitrypsin deficiency and other chronic nonalcoholic liver disease)

Reviewer's Comment: As shown above, the investigators included multiple potentially disparate clinical entities as evidence of baseline liver disease or evidence of hepatic dysfunction. This results in substantial clinical heterogeneity amongst these individuals. See more in Discussion.

Exclusion Criteria

- Had been prescribed a statin at any time during the 365 days prior to enrollment
- Had a history of any of the following diagnoses prior to enrollment

Diagnosis

- Drug-induced liver disease with
- Disorders of bilirubin excretion (without elevated LTs or other liver-disease diagnosis)
- Cancer (except non-melanoma skin cancer)

Reviewer's Comment: Some patients with drug induced liver disease and a benign disorder of bilirubin excretion were excluded, limiting the evaluation of drug effects in this subset of the population.

2.2 Study Period:

The study period was from January 1, 1995 to June 30, 2004. Eligible patients were required to have lovastatin exposure at enrollment, defined as receipt of a lovastatin prescription as documented in the KPNC automated pharmacy database.

2.3 Study Outcome**:**

Primary Endpoint:

The study's primary outcome variable was Hy's rule (defined as the presence of a serum ALT> 3 times the upper limit of normal (ULN), a serum total billirubin > 2X ULN **and** a serum alkaline phosphatase ≤ 1.5 times the ULN.

Secondary Endpoint:

The first occurrence any of the following

- Liver injury (an increase in serum ALT to 3X the ULN **or** elevation of serum billirubin at least 3x/the ULN)
- Cirrhosis defined as the presence of diagnosis in the automated medical records
- Liver failure: a diagnosis in the automated medical records (portal hypertension, impaired hepatic synthetic function)

2.4 Data Analysis:

After screening and application of all the inclusion and exclusion criteria, the observational cohort was composed of 13,491(14.5%) lovastatin exposed and 79,615 non-lovastatin exposed patients for analysis. The predictor variable, exposure to lovastatin, was defined as receipt of lovastatin prescription as documented in the KPNC pharmacy database.

Incidence rate ratios and multivariate analyses were performed for lovastatin exposed and unexposed time periods.

Reviewer's Comment: The study was designed to estimate incidence rates. However, in order to estimate the incident rates (new cases of pre-specified outcomes after initiation of therapy), the study excluded existing pre-specified outcomes (prevalent cases) from analysis. Exclusion of prevalent outcomes from analysis may result in underestimating the effect of lovastatin on pre-existing cases

2.5 Results:

Study population consisted of 13, 491 (14.5%) patients with lovastatin exposure and 79,615 without exposure during the study period. The mean exposure time was 276 days (approximately 9 months). The lovastatin-exposed cohort was older, had slightly greater proportion of men, and had a greater burden of illness in comparison to the lovastatin – unexposed cohort.

Reviewer's Comment

The observed differences between the groups are expected as these attributes suggest patients at risk for preexisting cardiovascular disease.

Table1. Baseline characteristics of study sample

	All patients	**Ever Lovastatin Exposed**	**Never Lovastatin Exposed**	**p-value**
Number	93,106	13,491(14.5%)	79,615 (85.5%)	
Age, years	48.4	53.9	47.5	<0.0001
Men (N (%)	56,900(61%)	8,394(62%)	48,506(61%)	0.004
Length of Follow-up, months (interquartile range)	28.8 (12.1-58.2)	36.0 (16.0-62.0)	27.9(11.5-57.4)	<0.0001
Median Lovastatin Exposure,, months (interquartile range)		9.1 (4.3-19.1)		

Primary outcome analysis (Hy's Rule)

The number of Hy's rule events observed during the study period in the lovastatin exposed group was rare creating difficulty in data analysis. There were only 8 events of Hy's rule observed in the lovastatin exposed group for incidence rate of 1.69 per million person-days compared to 616 events in the non-exposed group for an incidence rate of 6.13 per million person-days. The calculated incidence rate ratio (IRR) was 0.28 (95% CI 0.12 to 0.55). (Incidence rate ratios defined as rates of lovastatin -exposed person-time compared to non-lovastatin exposed person time). These data are shown below as reprinted from Table 1 within the Sponsor's study report.

Table 2 from the Sponsor's study report:

Univariate person-time results for primary and secondary outcomes. Incidence rates (IR) are expressed in events per million person-days. Incidence rate ratios (IRR) refer to rates of lovastatin exposed person time compared to non-lovastatin exposed person time.

	Exposed Person-time			**Unexposed Person-time**				
Outcome	# Of events	Person-days of exposure	IR*	# of Events	Person-days of exposure	IR*	IRR	95% CI for IRR
Hy's Rule	8	4720423	1.69	616	100465184	6.13	0.28	0.12-0.55
Combined	201	3823746	52.5	7751	71100756	109	0.48	0.42- 0.55
Individual								
Liver injury	177	3969931	45.0	6661	74556876	89.3	0.5	0.43-0.58
Cirrhosis	39	4595492	8.4	3173	94110766	33.7	0.25	0.18-0.34
Liver Failure	24	4696685	5.1	2402	98270935	24.4	0.21	0.13-.031

*per million person-days

Secondary Outcome analysis:

For the combined secondary outcomes, exposure to lovastatin associated with reduction in the risk of any secondary outcome (IRR= 0.48, 95% CI 0.42 to 0.55)

The crude IRR for lovastatin with liver injury endpoint was 0.5 (95% CI 0.43 to 0.58) for the exposed compared to non- exposed. Similar risk reductions were observed with cirrhosis and liver failure endpoints.

Lovastatin-Discontinuation Sub study;

To assess the potential bias of clinicians discontinuing lovastatin use in patients with baseline liver disease, the study examined the rate of lovastatin discontinuation among subjects with LDL cholesterol > 160 mg/dL and baseline liver disease as defined by the investigators. The frequency of lovastatin discontinuation was examined across subgroups defined by baseline "liver-disease confidence" in patients with hypercholestrolemia. The first strata (group 1) were comprised of cohorts with liver disease diagnosis and elevated function test on at least two occasions. The second group, defined as having weaker evidence of liver disease, had either the presence of a liver – disease diagnosis with no liver function test abnormalities (Group 2a), or the absence of a liver-disease diagnosis but history of elevated liver test. Members with neither a liver-disease diagnosis nor liver function test abnormalities were then matched (2:1) with a member of one of the other four groups according to the length of follow-up and calendar date at the end of each patients follow-up. Discontinuation is defined as the absence of lovastatin prescriptions following the index date for those patients who were taking lovastatin prior. Discontinuation rate were compared across strata.

Table 3. Rates of lovastatin discontinuation by level if liver disease confidence . % Discontinuation refers to cumulative incidence of discontinuing receipt of lovastatin after index date for liver disease patients (groups 1 and 2) or a marched time point for patients without liver disease (group 3)

LT=Liver-function test abnormality(AST and/or ALT)

			Lovastatin Use		
Group	Category	N	Before index date	After index date	% discontinuation
1	Liver Dz & ≥ 2 LT	6391	2746	2399	12.6%
2a	Liver Dz only	6963	2654	2181	17.8%
2b(i)	≥ 2 LT only	3379	21102	16101	23.7%
2b(ii)	≥ 1 LT only	100496	51079	42216	17%.
3	No dx or LT abnl	294017	115043	96353	16.2%

Reviewer's comments: This analysis shows that there are some differences in the rate at which lovastatin was discontinued among these subgroups. Those with the most "convincing" evidence of baseline liver disease showed the lowest rate of discontinuation (12.6%) and the highest discontinuation rate was observed among patients with persistently elevated LTs. The reason could be that LT abnormalities are easily detected during visits as opposed to other liver disease categories. In addition, the sub-groups as defined by the investigators may lack clear and meaningful clinical significance. However, the overall discontinuation rate for all exposed groups with liver disease appears significantly higher in comparison to those exposed to lovastatin but apparently free of liver disease or LT abnormalities

Interestingly, only 2,746 (43%) of the 6,391 hypercholesterolemic members with both a liver-disease diagnosis and persistent LT elevations were taking lovastatin. The fact that 57% of hyperchlestrolemic patients with liver disease were not on lovastatin therapy is suggestive of channeling bias (or bias by diagnosis). The finding is supported by increased laboratory monitoring of liver enzymes in the patients with liver disease compared to patients with no disease.

3.1 Additional Commentary and Discussion:

A randomized, prospective study would have been the optimum study to evaluate the safety concern in this population. However, factors such as expense, ethical issues of use of placebo patients and the fact that these drugs have been in use for many years without significant overall safety concern may be an impediment to conducting such studies.

Observational studies have a number of limitations and, are prone to confounding of observed association. Some of the observed association may be explained by effect modifiers such as age, gender, general health status of the cohort, concomitant medications and others.

The submitted observational, retrospective, cohort study was conducted to assess the potential safety concern of lovastatin use in subjects with pre-existing liver disease. As noted above, there is considerable heterogeneity among this cohort. This represents a significant limitation to the study. The study would be substantially more robust with application of a more specific diagnosis of baseline liver injury OR stratification of the present cohort. For example (see table 4), patients with the baseline diagnosis of fatty liver disease (FLD) had the least observed (3/209) outcome events. Whereas the baseline diagnosis viral hepatitis and abnormal liver function test were observed with the most combined outcomes. The small observed outcome events with baseline FLD diagnosis supports the prevailing hypothesis that statin therapy in patients with FLD is safe[1] and may also be beneficial.[2]

Table 4. Combined outcomes for Baseline Diagnosis

	Exposed Events	***Unexposed Events***
All outcomes	*209*	*8367*
Hy's Rule	*8*	*616*
Baseline Diagnosis		
Viral Hepatitis	*36*	*3448*
ALD	*17*	*821*
FLD	*3*	*77*
Other Diagnosis	*29*	*1200*
Abnormal LTs	*124*	*2205*

Abbreviations:

ALD: Alcoholic Liver Disease

LTs: Liver Function test

FLD: Fatty Liver Disease

The study has the following additional limitations:

- *The analysis defined lovastatin as dichotomous exposure (as either present or absent) without taking dose, cumulative dose, or cumulative exposure into consideration. This may result in the study's limitation to predict outcome of longer continuous lovastatin exposure in patients with liver disease*

- *Very few Hy's Rule (n=8) events were found during the lovastatin exposure period. The result of this rare primary outcome may have created a problem to use a regression modeling which assumes large sample sizes. In addition, the study was designed to estimate incidence rates and excluded prevalent case. By excluding pre-existing Hy's rule case, the effect on lovastatin on pre-existing cases may be underestimated.*
- *Surveillance or detection bias (patients with liver disease may be more likely to be monitored) was found more liver enzyme testing among lovastatin treated patients resulting in differential monitoring.*
- *The degree of misclassification may affect the results*
- *Fatty liver diagnosis: The estimated incidence of fatty liver in patients with hypercholesterolemia is about 33%. In addition, fatty liver is also associated with diabetics and obese subjects. The clinical diagnosis of fatty liver is protean. The study attempted to validate the fatty liver diagnosis by conducting a fatty liver algorithm. 1061 charts that contained fatty liver diagnosis were reviewed. Of these, 113 (10.7%) were deemed as definitely meeting criteria for fatty liver, while 851 (80.2%) were found to carry the "probable "diagnosis of fatty liver. Ninety (8.4%) had no evidence to support the diagnosis and 7(0.7%) could not be classified. Therefore, according to the study over 90% were found to have either a "definite" or "probable" diagnosis, resulting in high positive predictive value of the clinical diagnosis. Therefore, the limitation with identification and coding of fatty liver and cirrhosis may affect the outcome of results*
- *The potential of health modifier effect (subjects who adhere to treatment have better outcomes) can not be properly evaluated in the study*
- *The current study assumes that lovastatin prescription as being the same as medication consumption without any consideration for medication adherence. This assumption can introduce bias with regard to medication compliance and exposure to lovastatin. For example, subjects with liver toxicity experiencing the usual symptoms of nausea and vomiting may be reluctant to continue oral*

medications for a period of time, hence limiting drug exposure. Additional outcome data of lovastatin prescription with cholesterol reduction would have been helpful in support of medication adherence.

4.0 CONCLUSIONS AND RECOMMENDATIONS

A randomized prospective study would be an optimum study to evaluate the potential hepatic risk of lovastatin use in patients with pre-existing liver disease. Identification of a cohort by specific types of baseline liver disease was not included. The heterogeneity introduced by the inclusion criteria used by the investigators represents a significant limitation to the study. The reviewed retrospective cohort, observational study has a number of other limitations inherent with such study designs. The study has conducted a number of sensitivity analysis and sub-studies to assess for potential biases and confounding. However, given the nature of the study design the potential contribution of confounding by diagnosis, misclassification, differential monitoring, and cumulative exposure to the outcome of the study results can not be fully ascertained. For example, there may be a higher rate of lovastatin discontinuation in patients with liver disease diagnosis and abnormal liver enzymes as compared to patients with no liver disease diagnosis and normal liver enzymes. The sub study of lovastatin discontinuation rate showed that about 57% of hypercholestrolemic patients with liver disease and or liver function test abnormalities were not taking lovastatin is suggestive of confounding by contraindication or challenging bias.

Although, the results of the study (within the limitation of observational study) are consistent with the results of other published studies[3], a pooled analysis[4] of clinical trials, post marketing studies[5, 6], and opinion of clinicians,[7] by itself, this study does not definitively show that the risk of serious liver injury as defined by the investigators, in lovastatin exposed patients with some baseline liver disease is not greater when compared to those non exposed.

Shewit Bezabeh MD, MPH

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/s/

Shewit Bezabeh
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MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-213
Submission Code	000 AZ
Letter Date	August 24, 2004
Stamp Date	August 25, 2004
PDUFA Goal Date	February 24, 2005
Reviewer Name	Daiva Shetty, MD
Review Completion Date	January 28, 2005
Established Name	Lovastatin
(Proposed) Trade Name	Mevacor™ Daily
Therapeutic Class	Cholesterol reducer
Applicant	Merck & Co., Inc.
Priority Designation	S
Formulation	20 mg Tablet
Dosing Regimen	One tablet daily
Indication	Cholesterol reducer
Intended Population	Men 45 years or older Women 55 years or older

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

In the opinion of this reviewer, based on the many unanswered questions in the data of the Actual Use study CUSTOM, the application to switch lovastatin 20 mg tablets from prescription (Rx) to over-the-counter (OTC) status is not approvable.

There are many unresolved issues of self-diagnosis, self-selection, de-selection, efficacy, and safety (especially with regard to the Pregnancy Category X status and unresolved issues with liver function test monitoring). These unresolved issues leave the risk-benefit assessment of Mevacor™ 20 mg as an OTC product for prevention of Coronary Heart Disease (CHD) in the target OTC population, unresolved as well.

1.2 Recommendation on Postmarketing Actions

No recommendations on postmarketing actions would be appropriate at this time.

1.2.1 Risk Management Activity

No recommendations on the need for post-marketing risk management activities would be appropriate at this time.

1.2.2 Required Phase 4 Commitments

No recommendations on the need for Phase 4 commitments would be appropriate at this time.

1.2.3 Other Phase 4 Requests

No recommendations on other Phase 4 requests would be appropriate at this time.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The sponsor is seeking to market MEVACOR™ Daily 20 mg tablet as a cholesterol reducer for men (45 years of age and over) and women (55 years of age and over) with low density lipoprotein cholesterol (LDL-C) between 130 and 170 mg/dL, who also have one or more additional risk factors for coronary heart disease. This subset of individuals falls into a primary prevention of CHD population with less than a 20% 10-year CHD risk.

This is the sponsor's second attempt to switch Mevacor from Rx to OTC status. The original NDA 21-213 sought to switch lovastatin 10 mg from Rx to OTC status and was submitted on December 10, 1999. In support of the Rx-to-OTC switch, the sponsor submitted the results of seven clinical studies: four in-home "Use" studies, one placebo-controlled double-blind efficacy study, two pharmacokinetic studies, and three label comprehension studies. The data were presented at the Advisory Committee on July 13, 2000. The NDA was found to be non-approvable, based on the data reviewed. Several deficiencies were raised by the Agency in the October 6, 2000 not approvable (NA) letter:

1. Neither the rationale for treating the proposed target population with Mevacor 10 mg in the OTC setting, nor a favorable benefit/risk ratio for such treatment has been adequately established.
2. The data did not demonstrate that consumers can understand and adequately implement treatment to a defined goal or that there is an identifiable population of consumers for whom treatment with a fixed dose of Mevacor, without titration to reach a treatment goal, would represent an acceptable standard of care.
3. Consumers' ability to self-select and adequately comply/adhere with chronic therapy, as well as recognize the risks of therapy, was not demonstrated.
4. The sponsor did not provide adequate justification for deleting the recommendation for hepatic transaminase monitoring for Mevacor 10 mg when used in the OTC setting.
5. The data did not adequately demonstrate the ability of consumers to comprehend the risks associated with concomitant use of Mevacor with numerous interacting drugs.
6. The sponsor has not adequately addressed the risks to the fetus of potential Mevacor use by women who are pregnant or of childbearing potential in the OTC setting.
7. The product name, Mevacor CC, was not acceptable.

The current submission is the sponsor's complete response to the October 6, 2000 NA letter. In support of this new proposal, the sponsor has submitted the following for the Agency review:

1. Revised target population
2. Revised dosing directions
3. Actual Use Study (Protocol #084)
4. Label Comprehension Study (Protocol #90-NG)
5. Proposed labeling and other marketing tools
6. Reanalysis of AFCAPS/TexCAPS data.
7. In support of revising the liver function test recommendations in the prescription lovastatin label, information was submitted to the prescription MEVACOR™ NDA 19-643.
8. The sponsor requested to change lovastatin's Pregnancy Category from X to C. The data to support this request was submitted to the prescription MEVACOR™ NDA 19-643. The request was subsequently denied by the Agency.
9. In addition to the new information, the sponsor has resubmitted information from several other previously submitted and reviewed studies.

The Center for Drug Evaluation and Research (CDER) Reviewer's template headings does not comfortably lend itself to the review of an actual use study. Thus, the details of the protocol and

issues of self-selection and compliance are reviewed under Section 6, the Integrated Review of Efficacy. Safety issues are addressed under subheading 7, Integrated Review of Safety. The results are briefly summarized in the respective sections under this section 1.3 (Summary of Clinical Findings).

1.3.2 Efficacy

The efficacy of lovastatin as a cholesterol reducer was established in several placebo-controlled efficacy trials during its development as prescription drug. To support the efficacy of the 20 mg dose in the targeted OTC population, the sponsor reanalyzed the data from the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). This reanalysis is under review by the Division of Endocrine and Metabolic Drug Products.

In addition, the sponsor conducted one actual use study entitled: **A Consumer Use Study of OTC MEVACOR™ (CUSTOM): A 6-Month Consumer Behavior Study of the MEVACOR™ OTC Self-Management System (# 084).**

The objective of the actual use study was to determine, if the MEVACOR™ OTC (MOTC) Self-Management System enables consumers to appropriately manage elevated cholesterol levels, and to assess the safety and tolerability of MEVACOR™ OTC in a population who chooses to self-medicate. This was an open-label, uncontrolled, "all-comers," multi-center 6-month duration actual use study in a simulated OTC setting, which was not completely reflective of the current marketplace. Participants were recruited by using an advertisement targeted to consumers who knew their cholesterol numbers. All participants were pre-screened by phone prior to enrollment at the study site. The study sites were set up in a pharmacy setting with access to cholesterol testing and a nurse investigator to assist at the time of purchase.

Study Results

A total of 3316 subjects participated in the purchase-decision part of the study. Of those, 1205 (36.3%) made a decision to purchase the product. The most common reason for not purchasing the study medication was that participants needed more information (62.5%) or to talk to their physician (46.2%). Three subjects were excluded because they had ALT values >3x ULN.

One thousand sixty one (1061) subjects used the study medication. Two of them were found to be protocol violators and therefore were excluded. The remaining 1059 participants were considered as the population of Users. Seven hundred and one (66.1%) Users completed the study.

Demographic data show that a significant proportion of African Americans, compared to Caucasians, called but decided not to use the drug. Of the 2298 African Americans who contacted the call center, 632 (27.5%) showed up at the enrollment site and only 90 (3.9%) purchased and used the drug. Out of a total of 7674 Caucasian callers, 2393 (31.8%) came to the enrollment site and 869 (11.3%) purchased and used the drug. A low literacy population comprised 12.8% of all Users. Among the 1061 subjects, who purchased and used the study drug, 430 (40.5%) were females and 631 (59.5%) were males.

Self-Selection Assessment

According to the proposed label, there are 4 conditions that determine correctness of the self-selection, and the hierarchy of a thought process that consumers have to go through when looking at the label is as follows:

1. Age: **only** for men 45 years or older or women 55 years or older,
   plus
2. LDL-C level **only** between 130 and 170 mg/dL,
   plus
3. One or more of the following risk factors for CHD:
   - Smoking
   - High blood pressure
   - Family history of CHD
   - HDL-C 1 to 39 mg/dL

   plus
4. Absence of conditions that may put the user at increased risk of an adverse experience (liver disease, high triglycerides, history of statin induced muscle pain)

The number of study participants fitting these criteria is low: only 110 (10%) out of the 1059 Users. The majority of these (N = 77) were men. Only 33 of the women Users in the study met these criteria.

Out of the 430 women who purchased and used the study drug, 269 met the age criteria (≥ 55 years), of those 100 had baseline LDL-C between 130 and 170 mg/dL, and 69 had one or more risk factors for CHD.

Male Users were older and had a higher number of risk factors for CHD. Out of the 629 male Users, 530 met the age criteria (≥ 45 years), of those 181 had baseline LDL-C between 130 and 170 mg/dL, and 137 had one or more CHD risk factor.

If we exclude 3 subjects with underlying liver disease (1 man and 2 women) and 18 (11 men and 7 women) subjects with a history of muscle weakness from taking statin, the numbers are 60 women and 125 men. There were 16 out of 60 women and 6 out of 125 men, who had only one risk factor for CHD in addition to the age and a high level (> 60 mg/dL) of HDL-C. According to NCEP guidelines, HDL-C above 60 mg/dL is a "negative" risk factor for CHD, i.e., one other factor can be negated by a high HDL-C level, and therefore, these 22 Users are not in the target population for Mevacor OTC therapy. Finally, there were 53 Users (11 women and 42 men) with a high triglyceride levels (> 200 mg/dL). The final numbers of correct self-selectors according to the strict label eligibility criteria becomes 33 women and 77 men. It is unclear which of them consulted a physician prior to the use of Mevacor. The flow chart below gives a summary of the self-selection according to the proposed OTC label data.

Total Users (N=**1059**: 430 women and 629 men)

↓ → Did not meet age criteria:

Met age criteria 161 women

269 women (≥ 55 years)		99 men
530 men (≥ 45 years)		
↓	→	LDL-C not within 130-170 mg/dL
LDL-C within 130-170 mg/dL		169 women
100 women		349 men
181 men		
↓	→	≤ 1 risk factor for CHD
> 1 risk factor for CHD		31 women
69 women		42 men
137 men		
↓	→	+ liver disease
No Liver disease		2 women
67 women		1 man
136 men		
↓	→	+ history of muscle weakness
No history of muscle weakness		7 women
60 women		11 men
125 men		
↓	→	1 CHD risk factor and HDL-C > 60 mg/dL
HDL-C < 60 mg/dL		16 women
44 women		6 men
119 men		
↓	→	TG ≥ 200 mg/dL
TG < 200 mg/dL		11 women
33 women		42 men
77 men		

The sponsor estimated that > 80% of subjects would make a correct self-selection decision, > 75% would correctly de-select by Week 6, and > 75% would correctly de-select by Week 26. Results of the study, **based on the sponsor's primary analyses**, show that those percentages were 55.1% (n = 571), 41.3% (n = 409), and 50.1% (n = 494), respectively. Of the 571 appropriate self-selectors, who by the sponsor's definition adhered to the label, only 68 made a decision on their own; 416 subjects stated that they talked to their physician, and 87 did not completely meet label eligibility criteria but did not have risk conditions for the treatment. Even though a physician's advice to continue or discontinue the drug therapy is a valid justification for deviation from the label use directions, this is not always available in the over-the-counter setting. We cannot estimate the real rate of consumer contact with a health care provider during this study, because the contact itself, and the information discussed with a health care provider, were not verified by the study personnel. In addition, information as to whether participants actually had a personal health care provider or health insurance was not collected. Therefore, we cannot assess how the behavior of people with and without the access to health care would have differed.

The most common reason for failure in self-selection was that participants did not know their cholesterol levels. Of those subjects who stated that they knew their cholesterol levels, only half

identified their LDL-C level correctly. Even though 188 (18%) did not know their complete lipid profile, they chose to use the drug. Elevated triglycerides (> 200 mg/dL), one of the "do not use" conditions on the label, were present in 170 participants (16% of all Users).

Of the 1061 Users (including the 2 protocol violators mentioned on page 6), 589 (55.5%) had one or more medical risks specified on the MOTC study label. In addition, 23 (2.2%) subjects' self-selection status was not known due to missing information. This brings the number to only 449 (42.3%) Users who did not have risks for using MOTC 20 mg.

There was a notable difference between men and women in the distribution of CHD risk. A total of 51.2% of the women had 10-year risk for hard CHD that was less than 5% compared to 11.0% of the men. In contrast, 59.5% of the men fell in the 5% to 25% range compared to 28.1% of the women falling in this range. The sponsor calculated that 289 (27%) Users had a 10 year CHD risk of < 5%.

The sponsor included several post-hoc analyses to determine if consumers that chose the product were appropriate for cholesterol reduction therapy. One such analysis was the "closely adhered to label benefit criteria". This category included individuals who did not meet the label defined ranges for age, LDL-C, HDL-C or number of CHD risk factors, but who knew their lipid profile, had a self-reported TG < 200 mg/dL, did not substitute MOTC for their prescription cholesterol lowering medication, and did not have diabetes, heart disease, or stroke. By this definition, an additional 115 Users were added to the appropriate self-selection group of 571 (a total 686). Further, the sponsor analyzed the 10-year risk for myocardial infarction or coronary death, based on measured lipid levels, and found that 258 of those subjects were eligible for statin therapy according to ATP III. As a results of these numeric adjustments, the final initial appropriate self-selection rate rose from 55.1% to 89% (944 of 1059 users).

These post-hoc analyses are not based on the subject's self-selection decision but rather on the retrospective analyses of their baseline characteristics. Consumers will not be assessing their 10-year risk for CHD at the time of purchase. They should be able to make a correct self-selection decision by reading the label.

Compliance with the Follow-up Cholesterol Test

Compliance with the follow-up cholesterol testing was relatively high: 666 (63%) of the 1059 Users had a follow-up test during the 6 months of the study; 346 (32.7%) had it within the specified time interval of 4 to 12 weeks.

There were numerical differences among the analyzed demographic subgroups; none of them were statistically significant. With respect to the initial use decision and follow-up cholesterol test, greater percentages of elderly Users compared to those < 65 years of age, and normal literacy compared to low literacy Users, adhered to label benefit criteria. More Caucasians compared to non-Caucasian Users adhered to the label benefit criteria in respect to follow-up cholesterol testing.

LDL-C Reduction in User Population

The median reduction in LDL-C achieved in the population who used MOTC was 20.6%. Further reduction, 25.2%, was observed in the cohort of 243 Users that fasted at baseline and at the end of study.

A total of 282 (26.6%) Users achieved the LDL-C goal of < 130 mg/dL within 4 to 12 weeks. According to the sponsor's definition, of the 878 Users with a known LDL-C value at the end of the study and who had a known LDL-C value at baseline, 548 (62.4%) achieved the LDL-C goal (< 130 mg/dL) by the end of the 6-month study. This number, in actuality, includes 160 Users whose LDL-C level at baseline was < 130 mg/dL and 39 Users whose LDL-C level at baseline was unknown. We do not know what benefit, if any this subpopulation derived from the treatment. If we deduct these 199 (160+39) Users, the percentage of Users achieving benefit by the end of the study decreases to 39.7% (349/878).

Out of a total of 484 subjects initially self-selecting according to the label criteria (based on the sponsor's DAP (Data Analysis Plan) analysis), 297 achieved LDL-C goal (< 130 mg/dL) at the end of the study. Thirty-nine of these 297 participants discontinued the study for various reasons. Sixty-eight participants initially self-selected correctly according to the label criteria without a physician interaction. They are a subset of the above 484. Of these 68 participants, 41 achieved their LDL-C goal (< 130 mg/dL) at the end of the study. Thus, of the 1059 Users, 41 (4%) correctly, independently achieved the target LDL-C < 130 mg/dL.

1.3.3 Safety

All 1061 Users who reported taking at least one dose of study medication were included in the assessment of safety. The mean duration of exposure to lovastatin 20 mg "based on the therapy stop date" was 148.3 days (range 1 to 290 days).

The methodology to assess drug exposure is flawed. The study duration was relatively short considering the labeled indefinite use of the drug. There were no diaries used in the study. Data on drug accountability was not provided by the sponsor. The study drug stop date was not collected; therefore, the amount of time that participants had study drug in their possession was used as a surrogate for the therapy stop date in the calculation of actual duration of treatment.

Overall, 452 (42.6%) participants had at least one adverse experience; of these, 180 participants had drug-related experiences as determined by an investigator. Twenty-eight participants reported serious adverse experiences, one of which was drug related. Seven of the 28 discontinued from the study due to the serious adverse experiences, one of which was drug-related.

One of the non drug-related serious adverse experiences resulted in death. The reported case of death was due to a massive stroke, and the reporting physician determined that the massive stroke and subsequent death were probably not related to study drug therapy.

A total of 360 (33.9%) subjects out of the 1061 Users discontinued prior to the end of the study. One hundred twenty-five (11.8%) reported that they discontinued therapy due to a clinical adverse experience, of which, 102 (9.6 %) adverse experiences were considered by the study investigator to be drug-related. As mentioned above, seven (0.7%) participants discontinued study therapy due to serious adverse experiences one of which was drug-related. Fifteen participants reported discontinuation of therapy due to a clinical adverse experience but were counted as completers of the study because they returned for their final scheduled visit. Adverse experiences resulting in discontinuation most often occurred in the Musculoskeletal and Connective Tissue Disorders (6.3%) and Gastrointestinal Disorders (2.8%) Categories. The most frequently reported adverse experiences resulting in study therapy discontinuation were Myalgia (3.7%) and Arthralgia (1.2%).

There was a low incidence of drug-related clinical adverse experiences in each body system category except for "Musculoskeletal and Connective Tissue Disorders (8.8%)," and "Gastrointestinal Disorders (5.4%)." The most frequently reported drug-related clinical adverse experiences were myalgia (5.4%), flatulence (1.7%), arthralgia (1.5%), headache (1.2%), and muscle weakness (1.1%). CPK levels were not measured; this is one of the deficiencies of the study.

Five (0.5%) of the participants had one or more laboratory adverse experience during the study. Four of the 5 participants had a laboratory adverse experiences that was determined by the investigator to be drug-related. An increased ALT was to be reported as a laboratory adverse experience if it was > 3 x ULN (120 U/L). Increased ALT (Normal Range 10-40 U/L) was the most frequent laboratory adverse experience reported, occurring in four of 986 (0.4%) participants who had a laboratory test post baseline. One participant, discontinued due to an increased ALT of 59 U/L (ULN = 40 U/L), and an increased AST of 53 U/L (ULN = 40 U/L), both reported by a study investigator as possibly related to study drug therapy. No post-discontinuation follow-up was required as per protocol. Three (3) of 986 (0.3%) of the total user population had an increased ALT that was > 3 x ULN at the end of the study. All 3 of them had a repeat ALT; two on the repeat test had values below 1 x ULN and the third had a value of 43 U/L.

Data on lovastatin overdose supports its wide margin of safety. To date, there are no deaths reported due to a single high overdose of lovastatin.

1.3.4 Dosing Regimen and Administration

The proposed nonprescription dose of lovastatin is 20 mg once daily with the evening meal. Single daily doses of lovastatin given with the evening meal are more effective than the same dose given in the morning. The usual recommended prescription starting dose is 20 mg daily with the evening meal and the dose can be adjusted upward as needed to achieve the target cholesterol level. For reasons already mentioned, whether this proposed fixed OTC dosing regimen results in an acceptable risk/benefit ratio in the target population remains unresolved.

1.3.5 Drug-Drug Interactions

Several drugs (cyclosporine, clarithromycin, itraconazole, ketoconazole, nefazodone, erythromycin, and HIV protease inhibitors) have the potential to interact with lovastatin when administered concomitantly. These drugs and grapefruit juice, are strong CYP3A4 inhibitors, and may increase plasma HMG-CoA inhibitory activity levels, and therefore may increase the individual's risk of myopathy. In addition, gemfibrozil and niacin may also increase the risk of myopathy through a different mechanism.

1.3.6 Special Populations

Fifty percent of women who enrolled in the actual use study were less than 55 years of age, and 37.4% of the women Users were less than 55 years. These data show poor understanding of the product use and failure in self-selection. This is of particular concern because lovastatin is a Pregnancy Category X drug.

The issue of liver toxicity also remains unresolved. It is unclear how asymptomatic consumers with LFTs 3x ULN would properly self-select not to use Mevacor and whether they would be harmed if they took the drug.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Mevacor™ (lovastatin), is a cholesterol lowering agent isolated from a strain of Aspergillus terreus. After oral ingestion, lovastatin, which is an inactive lactone, is hydrolyzed to the corresponding (beta)-hydroxyacid form. This is the principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate limiting step in the biosynthesis of cholesterol.

The sponsor is proposing to market Mevacor™ 20 mg tablet in the OTC setting for men 45 years and older and women 55 years of age and older, with LDL-C level between 130 mg/dL and 170 mg/dL, and additional one or more risk factors for CHD.

2.2 Currently Available Treatment for Indications

There are no OTC drugs currently available for the treatment of hypercholesterolemia. Current medical practice is such, that elevated serum cholesterol is treated based on the latest National Cholesterol Education Program (NCEP) Adult Panel Treatment Panel (ATP) III guidelines (Table 1, References 1 and 2).

Table 1. NCEP LDL-C Cholesterol Treatment Guidelines

Levels of LDL-C at which to consider Drug Therapy (mg/dL)			
	TLC*	**Drugs**	**Goal**
High risk: CHD or CHD risk equivalents (10 year risk >20%)	≥ 100	≥ 100	< 100
Moderately high risk: 2+ risk factors (10-year risk 10-20%)	**≥ 130**	**≥ 130**	**< 130****
Moderate risk: 2+ risk (10-year risk < 10%)	**≥ 130**	**≥ 160**	**< 130**
Lower risk: 0-1 risk factors	≥ 160	≥ 190	< 160

* TLC: therapeutic lifestyle changes; ** for moderately high-risk persons, when LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of available trial results.

According to the ATP III guidelines, elevated LDL cholesterol is the primary target of cholesterol-lowering therapy. Therapeutic lifestyle changes (TLC) are the essential initial step of therapy in all the risk categories.

Risk factors include:

- family history of premature coronary heart disease (below age of 55 years in a male parent or sibling or below 65 in female relative)
- hypertension (BP ≥ 140/90 mmHg or an antihypertensive medication)
- cigarette smoking
- diabetes mellitus
- low high density lipoprotein cholesterol (HDL-C) (< 40 mg/dL), and
- age (men ≥ 45 years, women ≥ 55 years).

HDL-C ≥ 60 mg/dl is a negative risk factor, i.e., one other factor can be negated by a high HDL-C level.

2.3 Availability of Proposed Active Ingredient in the United States

There are several HMG-CoA reductase inhibitors available as prescription drugs for the treatment of elevated serum cholesterol in the United States. This class of drugs is not currently approved for over-the-counter marketing.

2.4 Important Issues With Pharmacologically Related Products

There are several important safety issues with HMG-CoA reductase inhibitors with respect to over-the-counter marketing:

- Relative contraindications exist in patients taking specific concomitant medications (cyclosporine, gemfibrozil, niacin, macrolide antibiotics, various anti-fungal agents, and strong cytochrome P-450 inhibitors).
- Myopathy and Rhabdomyolysis. The estimated rate of myopathy with statin monotherapy is 0.025-0.5% and is dose-dependent. The risk of myopathy increases with concurrent use of other drugs ([especially strong Cytochrome P-450 3A4 inhibitors such as cyclosporine, itraconazole, and erythromycin] or gemfibrozil) and is also increased with frailty, the very elderly, individuals with a smaller body mass index, and multisystem disease (e.g., chronic renal insufficiency associated with diabetes mellitus). Routine measurements of muscle enzymes contribute little in preventing the possible development of myopathy. Following the voluntary market withdrawal of cerivastatin (Baycol) in 2001, the safety of statins as a class, especially with respect to the effects of statins on the liver and skeletal muscle were reevaluated. The rate of fatal rhabdomyolysis for cerivastatin was far greater than that for other statins (16 to 80 times higher). More than 60% of the fatal cases with cerivastatin were associated with use of the highest dose (0.8 mg daily). There did not appear to be any difference in the rate of fatal muscle complications among the 5 statins currently available in the United States (atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin).
- Hepatic Effects. There are 2 distinct and unrelated manifestations of statin-induced hepatic effects. The most common one appears to be a self-limited, reversible, dose-related elevation of ALT that is asymptomatic. The rare reports of acute liver failure associated with all statins may be due to an idiosyncratic reaction. Monitoring liver function tests for hepatotoxicity is currently recommended for all statins, including lovastatin.
- Pregnancy Category X. Lovastatin is contraindicated for use by pregnant or breastfeeding women. The Pregnancy Category X status was based on several preclinical studies. In a submission to the prescription lovastatin NDA 19-643/S-061 dated March 31, 2004 the sponsor requested to change lovastatin's Pregnancy Category from X to Category C. The request was denied due to insufficient data to support the change.

2.5 Presubmission Regulatory Activity

NDA 21-213 originally was submitted on December 10, 1999 by Merck & Co, Inc. and Johnson & Johnson Consumer Pharmaceuticals Co. requesting the Agency's approval to market 10 mg strength tablets of lovastatin as an OTC drug product. In support of the Rx to OTC switch, the sponsor submitted the results of seven clinical studies: four in-home "Use" studies (Protocols 076, 077, 079, and 081); one placebo-controlled double-blind efficacy study (Protocol 075); two pharmacokinetic studies (Protocols 078 and 082); and three label comprehension studies. The data were presented at the Advisory Committee on July 13, 2000. The NDA was considered not-approvable, based on the data reviewed. Several deficiency issues were raised by the Agency in the October 6, 2000 not approvable (NA) letter:

1. Neither the rationale for treating the proposed target population with Mevacor 10 mg in the over-the-counter (OTC) setting, nor a favorable benefit/risk ratio for such treatment has been adequately established.

2. The data did not demonstrate that consumers can understand and adequately implement treatment to a defined goal or that there is an identifiable population of consumers for whom treatment with a fixed dose of Mevacor, without titration to reach a treatment goal, would represent an acceptable standard of care.
3. Consumers' ability to self-select and adequately comply/adhere with chronic therapy, as well as recognize the risks of therapy, were not demonstrated.
4. The sponsor did not provide adequate justification for deleting the recommendation for hepatic transaminase monitoring for Mevacor 10 mg when used in the OTC setting.
5. Data did not adequately demonstrate the ability of consumers to comprehend the risks associated with concomitant use of Mevacor with numerous interacting drugs.
6. The sponsor has not adequately addressed the risks to the fetus of potential Mevacor use by women who are pregnant or of childbearing potential in the OTC setting.
7. The product name, Mevacor CC, was not acceptable.

Since the NA letter, there have been a series of communications between FDA and the sponsor on different aspects of the Mevacor Rx-to-OTC switch development program.

The current submission is the sponsor's complete response to the October 6, 2000 NA letter. In support of this new proposal, the sponsor has submitted the following for the Agency review:

1. Revised target population
2. Revised dosing directions
3. Actual Use Study (Protocol #084)
4. Label Comprehension Study (Protocol #90-NG)
5. Proposed labeling and other marketing tools
6. Reanalysis of AFCAPS/TexCaps data.
7. In support of revising the liver function test recommendations in the prescription lovastatin label, information was submitted to the prescription MEVACOR™ NDA 19-643.
8. The sponsor also requested to change the lovastatin's pregnancy Category from X to C. The data to support this request was submitted to the prescription MEVACOR™ NDA 19-643.
9. In addition to the new information, the sponsor has resubmitted information from several other previously submitted and reviewed studies.

2.6 Other Relevant Background Information

As of March 26, 2004, lovastatin has received marketing approval in 59 countries. It has been withdrawn from the market in 13 countries. None of the withdrawals were for safety reasons.

The only country where statins are available without a prescription is the United Kingdom. Simvastatin (Zocor Heart Pro) 10 mg tablets were reclassified from prescription to over-the-counter status (for sale in pharmacies) in May, 2004. Simvastatin 10 mg is indicated for men 45 years and over and women 55 years and over with one or more risk factors for CHD.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Review is pending.

3.2 Animal Pharmacology/Toxicology

There are no preclinical data submitted to this NDA.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

In support of the current resubmission, requesting to switch Mevacor™ 20 mg from Rx-to-OTC status, the sponsor provided results of one actual use study, an integrated summary of safety, and proposed OTC labeling which are being considered in this review. The label comprehension study is under review by Laura Shay, RN, MS, C-ANP in HFD-560. The reanalysis of AFCAPS/TexCAPS and LFT data are being reviewed by the Division of Endocrine and Metabolic Drug products. The pregnancy risk data submitted in March was already reviewed.

4.2 Tables of Clinical Studies

There is one new clinical study submitted for review to this supplemental new drug application: A Consumer Use Study of OTC MEVACOR™ (CUSTOM): A 6-Month Consumer Behavior Study of the MEVACOR™ OTC Self-Management System (Protocol # 084).

4.3 Review Strategy

This review covers the results of the Consumer Use Study of OTC MEVACOR™ (CUSTOM): A 6-Month Consumer Behavior Study of the MEVACOR™ OTC Self-Management System (#084). The study is not a controlled efficacy and safety trial, but instead is an actual use trial. Therefore, the content does not easily correlate with the headings of the CDER Clinical Review Template. The study design, methodology, consumer behavior and drug use data will be reviewed in the efficacy part of the template. Safety data gathered during the study will be included in the safety section of the review.

The study description (design, methodology, and results) in an abbreviated form were taken from the sponsor's submission of the NDA. The reviewer's comments are written in an italic font.

4.4 Data Quality and Integrity

The sponsor states that this study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

All study sites participating in the study were reviewed and approved by the Biomedical Research Institute of America (BIOMED).

4.5 Compliance with Good Clinical Practices

The sponsor states that Quality Control and Quality Assurance measures were followed as dictated by the appropriate department's Standard Operating Procedures. These activities included: on-site monitoring of investigator sites, on-site and in-house review of clinical study participant data, resultant data bases, and review of Clinical Study Reports.

Investigator meetings were held at the outset of the study to review all protocol procedures and investigator responsibilities under Good Clinical Practices. A pre-training meeting was held via videoconference within a month of the study start. Following this meeting, a 3-day Investigator's Meeting was held within a month of the study start. Regularly scheduled teleconferences were held during the study with AmeriTrial (site management contract research organization) and Telerx (management of toll-free product specialists, interactive response system (IVRS), web site, and Consumer Assistance Program fulfillment). In addition, during the conduct of the study the Merck clinical team held several teleconferences directly with study investigators, and issued numerous training updates to answer questions, clarify procedures, and respond to emergent data management issues. Study site activities and documents were monitored for quality and control on a regularly scheduled basis by Clinical Research Associates under the direction of AmeriTrial. A quality assurance audit of Telerx was performed by Merck Computer Validation Quality Assurance to ensure compliance with United States Code of Federal Regulations 21 CFR Part 11 regarding clinical data collection and management.

4.6 Financial Disclosures

The sponsor has submitted the Form FDA 3454 certifying financial interest by the investigators. There were a total of 14 primary investigators and 64 subinvestigators throughout 14 study #084 sites. Sixty-eight of the 80 participating investigators/subinvestigators provided their financial information and were certified by Merck regarding the absence of financial arrangements as defined in 21 CFR 54.2. The remaining 12 (15%) investigators participating in 5 study sites did not provide their financial information and were not certified. The sponsor states that multiple requests for the information were made, when possible, to clinical investigators who did not respond.

There were no DSI audits conducted for the study site or data analyses.

Comment:
Even though 15% of participating investigators did not provide their financial information, there are no data signals to suggest that the trial was conducted in a way to breach accepted ethical standards.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

There are no new pharmacokinetic data submitted to this NDA.

5.2 Pharmacodynamics

There are no new pharmacodynamic data submitted to this NDA.

5.3 Exposure-Response Relationships

There are no new data on exposure-response relationship submitted to this NDA

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor is seeking to market MEVACOR™ Daily 20 mg tablets as a cholesterol reducer for men (≥ 45 years of age) and women (≥ 55 years of age) with LDL-C between 130 mg/dL and 170 mg/dL, who also have one or more additional risk factors for coronary heart disease. This subset of individuals falls into a primary prevention of CHD population with less than a 20% 10-year CHD risk.

Comments:
Current clinical practice for the treatment of elevated serum cholesterol is based on the latest National Cholesterol Education Program (NCEP) Adult Panel Treatment Panel (ATP) III guidelines (See section 2.3 of this review). The sponsor's proposed targeted OTC population falls into a category eligible for drug therapy, and therefore, meets the ATP III guidelines for the treatment of hypercholesterolemia. It includes people in the moderate and moderately high risk for CHD category.

6.1.1 Methods

The efficacy of lovastatin as a cholesterol reducer was established in several placebo-controlled efficacy trials during its development as prescription drug. To support the efficacy of the 20 mg dose of lovastatin in the targeted OTC population, the sponsor reanalyzed the data from the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). This data re-

analysis is being reviewed in the Division of Metabolic and Endocrine Drug Products (HFD-510). The sponsor's findings from the reanalysis are summarized below. In addition to AFCAPS/TexCAPS data, the sponsor submitted results of the actual use study titled: **A Consumer Use Study of OTC MEVACOR™ (CUSTOM): A 6-Month Consumer Behavior Study of the MEVACOR™ OTC Self-Management System (# 084)**, which is being reviewed in detail throughout this document.

AFCAPS/TexCAPS, a double-blind, randomized, placebo-controlled, primary prevention study, compared treatment with MEVACOR vs. placebo in decreasing the rate of acute major coronary events (composite endpoint of myocardial infarction, unstable angina, and sudden cardiac death). The study had a median of 5.1 years of follow-up. Participants were men (ages 45-73) and women (ages 55-73) without symptomatic cardiovascular disease with average to moderately elevated total cholesterol (total-C) and LDL-C, below average HDL-C, and who were at high risk based on elevated total-C/HDL-C. In addition to age, 63% of the participants had at least one other risk factor (baseline HDL-C < 35 mg/dL, hypertension, family history, smoking, or diabetes). AFCAPS/TexCAPS enrolled 6,605 participants (5,608 men, 997 women) based on the following lipid entry criteria: total-C range of 180-264 mg/dL, LDL-C range of 130-190 mg/dL, HDL-C of $\leq$ 45 mg/dL for men and $\leq$ 47 mg/dL for women, and triglycerides (TG) of $\leq$ 400 mg/dL. Participants were treated with standard care, including diet, and either MEVACOR 20-40 mg daily (n= 3,304) or placebo (n= 3,301). Approximately 50% of the participants treated with MEVACOR were titrated to 40 mg daily when their LDL-C remained >110 mg/dL at the 20-mg starting dose.

MEVACOR reduced the risk of a first acute major coronary event, the primary efficacy endpoint, by 37% (MEVACOR 3.5%, placebo 5.5%; $p < 0.001$). A first acute major coronary event was defined as myocardial infarction (54 participants on MEVACOR, 94 on placebo) or unstable angina (54 vs. 80) or sudden cardiac death (8 vs. 9). Among the secondary endpoints, MEVACOR reduced the risk of unstable angina by 32% (1.8 vs. 2.6%; $p = 0.023$), of myocardial infarction by 40% (1.7 vs. 2.9%; $p = 0.002$), and of undergoing coronary revascularization procedures (e.g., coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 33% (3.2 vs. 4.8%; $p = 0.001$). Trends in risk reduction associated with treatment with MEVACOR were consistent across men and women, smokers and non-smokers, hypertensives and non-hypertensives, and older and younger participants. Participants with $\geq$ 2 risk factors had risk reductions in both acute major coronary events (43%) and coronary revascularization procedures (37%). Because there were too few events among those participants with age as their only risk factor in this study, the effect of MEVACOR on outcomes could not be adequately assessed in this subgroup.

Comment:
The AFCAPS/TexCAPS population is similar to the proposed target OTC population of consumers. The study demonstrates lovastatin's effectiveness in the studied population. There are two major issues that impact the applicability of these data to the OTC marketing proposal:

- *Pre-treatment LDL-C levels in the AFCAPS/TexCAPS population ranged from 130 to 190 mg/dL unlike the proposed OTC range of 130 and 170 mg/dL.*

- *The dose of Mevacor in the AFCAPS/TexCAPS study was titrated up in 50% of the cases. The proposed OTC lovastatin daily dose is fixed at 20 mg.*

More on the applicability of the AFCAPS/TexCAPS data to the proposed OTC population will be provided by reviewers in the Division of Metabolic and Endocrine Drug Products (HFD-510) who are assessing the data re-analysis submitted by the sponsor.

6.1.2 General Discussion of Endpoints

The remainder of Section 6 will focus on the Actual Use Study.

Title of the Study: A Consumer Use Study of OTC MEVACOR™ (CUSTOM): A 6-Month Consumer Behavior Study of the MEVACOR™ OTC Self-Management System (# 084)

Study Objectives and Hypotheses

Objectives

- To determine if the MEVACOR™ OTC Self-Management System enables consumers to appropriately manage elevated cholesterol levels.
- To assess the safety and tolerability of MEVACOR™ OTC in a population who chooses to self-medicate.

This study was primarily designed to evaluate the effectiveness of the MEVACOR™ OTC Self-Management System in guiding consumer behavior. The sponsor states that two facets concerning consumer behavior were of primary interest in this study:

- The initial self-selection decision to use the product, and
- The ongoing decision process regarding continued use (de-selection).

Based on the information collected from the participants, decisions were assessed on the day of first dose and at Weeks 6 and 26 (initial self-selection and de-selection decisions jointly), and were classified into ordinal categories. According to the initial protocol, those categories were:

- According to Label (AL) – this category represents a decision that is entirely consistent with the product label.
- Not According to Label, Medically Acceptable for Self-Management (NALMASM) - this category represents a decision that is not entirely consistent with the product label, but still results in a favorable benefit to risk ratio for the participant (achieve LDL-C goal of 130 mg/dL at 6 weeks).
- Not According to Label, Medically Unacceptable for Self-Management (NALMUSM) – this category represents a decision that is not consistent with the product label and would result in an unfavorable benefit to risk ratio for the participant.

The sponsor redefined these pre-specified categories after the study was in progress. The major difference that was introduced is the "physician override" concept. The categories used by the sponsor for the final analysis of data are as follows:

1. Medically Acceptable for Self-Management (MASM):
   - According to Label, Medically Acceptable for Self-Management (AL-MASM). This category represents a decision that is entirely consistent with the product label. Participants were also considered AL-MASM if their behavior was not entirely consistent with the label but they consulted with a doctor about their use of Mevacor OTC (MOTC) (a physician override).
   - Adequate Benefit, Medically Acceptable for Self-Management (AB-MASM). This category represents a decision that is not entirely consistent with the product label but use of the product still provides some benefit (i.e., lowering cholesterol) to the individual.
2. Medically Unacceptable for Self- Management (MUSM):
   - Not Adequate Benefit, Medically Unacceptable for Self-Management (NAB-MUSM). This category represents a decision that is not consistent with the product label and that deviates sufficiently that it allows potentially inadequate therapeutic benefit but without imparting undue potential safety risk. Some participants were placed in this category to self-manage their cholesterol levels either because their CHD risk was too low or too high.
   - Not Adequate Safety, Medically Unacceptable for Self-Management (NAS-MUSM). This category represents a decision that significantly deviates from the label directions, creating potential safety risks despite potential therapeutic benefit. It would be medically unacceptable for participants in this category to self-manage their cholesterol levels because of inappropriate safety decisions.

Primary Hypotheses

The sponsor states that the hypotheses of this study were constructed to evaluate whether a sufficient number of participants, while using the MEVACOR™ OTC Self-Management System, would make initial MASM self-selection and de-selection decisions. Of those who make an initial self-selection decision to use MEVACOR™ OTC:

- $\geq$ 80% will make an initial self-selection decision that is medically acceptable for self-management,
- $\geq$ 75% will make a final de-selection decision that is medically acceptable for self-management between the day of first dose and Week 6, and
- $\geq$ 75% will make a final de-selection decision that is medically acceptable for self-management between the day of first dose and Week 26.

Comment:
The sponsor states that the above mentioned benchmarks of $\geq$ 80%, $\geq$ 75%, and $\geq$ 75% were primarily based on the results of pilot label comprehension studies of the CUSTOM product label. However, the questionnaires, correct/acceptable answers, and the results of these pilot studies were not submitted with the application.

Secondary Hypotheses

The secondary hypotheses serve to further assess other aspects of the primary objective and also the safety and tolerability of MEVACOR™ OTC in a population who chooses to self-medicate:

- Of the users who take the End-of-Study Scenario Test, the proportion of responses that are medically acceptable for self-management will be ≥ 80% for each individual situation that should prompt a user to discontinue therapy or consult with a physician.
- MEVACOR™ OTC is well tolerated as measured by the incidence of adverse experiences in all users regardless of whether or not they made an appropriate self-selection decision.

Comment:
The End-of-Study Scenario Test was a group of consumer behavior questions administered at Week 26 or when a consumer chose not to repurchase Mevacor. It included a list of questions about the diagnostic material use, de-selection, adverse events, and reasons for inappropriate self-selection and de-selection.

6.1.3 Study Design

This was an open-label, uncontrolled, "all-comers," multi-center actual use study in a naturalistic OTC setting.

Recruitment
Participants were recruited by mass media advertising. The advertisement included a toll-free number for interested individuals to call for an appointment. The advertisements did not include any of the specific label inclusion/exclusion criteria. However, the advertisements stated that potential participants should know all 4 of their cholesterol numbers (i.e., Total-C, HDL-C, LDL-C, and triglycerides), even though knowledge of Total-C is not a criterion for product eligibility.

When they made the phone call, participants provided personal and demographic information (e.g., date of birth, gender, race, name, address) and were asked administrative exclusion questions. The telephone operator did not provide a reminder to bring cholesterol values; however, if a participant inquired about cholesterol testing at the site, they were told that they could purchase a test for $10 and that a fast of 9 to 12 hours prior to the test was advisable.

The operator advised interested participants that this study was designed to simulate a retail setting. Therefore, they were required to purchase study medication, but would be compensated for time and travel expenses.

Signs were posted in the storefront windows to attract potential participants as walk-ins. In order to track all participants in the database, walk-ins were required to call the toll-free study advertisement number from the site to be asked the administrative exclusion questions, and assigned a Participant Identification Number (PIN) even if the site had time for them to complete their first visit that day. If there was an immediate opening in the schedule, the participant provided requested information to the toll-free operator and then passed the phone to the investigator who recorded the PIN and demographic information on the site study record. The investigator then used the date-of-birth and gender information for the eligibility assessment if performed at the first visit. The eligibility assessment is discussed in detail below.

Inclusion Criteria
When participants called to make an appointment, they were included only if they said they could read and understand English without assistance.

Administrative Exclusion Criteria
1. Telephone Appointment Stage Exclusion Criteria
- Participant was currently or has recently (within 30 days of study start) participated in any clinical trial of an investigational or approved drug.
- Participant or household member was a physician or pharmacist, or was employed by a pharmaceutical company.
- Participant had participated in a clinical trial in which cholesterol medication was available only by purchase.

2. Storefront Visit (Following Purchase Decision), Exclusion Criteria
- Participant was a woman who indicated she was pregnant or breast-feeding.
- Participant had been told she/he had an allergy to prescription MEVACOR™.
- Participant had a baseline ALT value > 3 x ULN (only for purchasers who signed consent).

Overall Eligibility Assessment Based on Product Label
Eligibility for MEVACOR™ OTC was assessed using a scripted questionnaire and results were used for the analysis of self-selection and de-selection. The eligibility assessment was collected only one time, but could have been collected in one of three places (i.e., at the study site, through the toll-free product specialist/interactive voice response system (IVRS), or on the website). Participants who opted to use the toll-free product specialist/IVRS or website were informed if MEVACOR™ OTC was not right for them. They also learned their eligibility from the nurse investigator (acting as a pharmacist) if they asked for assistance at the first visit to the study site. Participants who did not avail themselves of these aspects of the MEVACOR™ OTC Self-Management System were administered the eligibility assessment at the end-of-study visit.

The following criteria had to be met in order for a participant to be considered eligible by the box label for MEVACOR™ OTC. An eligible participant:
- was a male ≥ 45 years (derived from date-of-birth given at initial phone contact; was not asked again on script),
- was a female ≥ 55 years (derived from date-of-birth given at initial phone contact; was not asked again on script),
- knew his/her LDL cholesterol was 130 mg/dL to 170 mg/dL,
- had one or more of the following risks for heart disease: hypertension, a family history of heart disease (heart disease in father or brother before 55 years of age or in mother or sister before 65 years), HDL ≤ 39 mg/dL, or was a smoker,
- was not currently taking one of the following prescription medications known to potentially interact with lovastatin: cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, nefazodone, gemfibrozil, or an HIV protease inhibitor,

- was not currently taking any prescription cholesterol-lowering medication, or prescription or nonprescription niacin (≥ 1000 mg/day),
- did not have active liver disease,
- had no history of heart disease (heart attack or angina), diabetes, or stroke,
- did not have triglycerides ≥ 200 mg/dL,
- did not have HDL ≥ 60 mg/dL, and
- had no history of muscle pain, weakness, or tenderness from taking a cholesterol-lowering medication.

Since this was an "all comers" study, ineligible participants (who did not meet the exclusion criteria) were not excluded from purchasing and using MEVACOR™ OTC for up to 6 months.

Figure 1 shows the general study procedures and procedures specific to visits. Table 2 lists a schedule of events specific to each visit. In addition, Figures 2 through 5 (Appendix I) taken directly from the sponsor's submission show study procedures for participants specific to:

- Storefront Visit (Figure 2)
- Follow-up visits to the Storefront for Purchasing Drug (Figure 3)
- Follow-up visits to the Storefront for Cholesterol Testing (Figure 4)
- Final Visit at the Storefront (Figure 5)

Figure 1. Overall Study Flow Chart

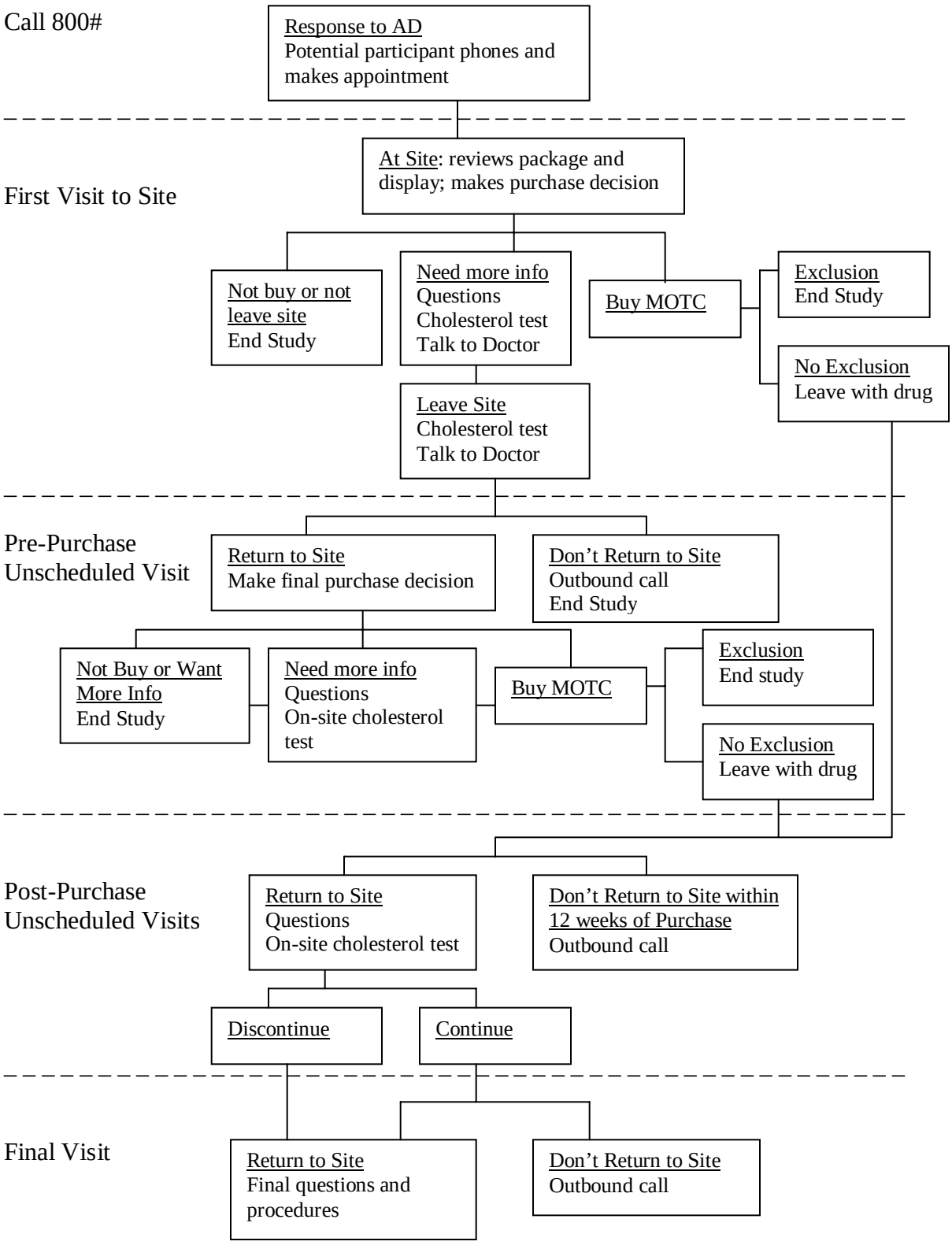


Table 2. Schedule of Clinical Observations and Laboratory Measurements

Activity	Pre-study	Day 1 Site Visit	Between Visits*	Follow-up Visits**	Final Visit
Demographics (collected by phone)	✓				
Participants read proposed OTC carton label and shelf signage		✓			
Participants made self-selection and purchase decision		✓		✓	
Participants who needed more information asked questions to investigator, left to talk to physician/get a cholesterol test and returned to make a decision		✓			
Collected lipid profile and ALT by Cholestech L·D·X™ fingerstick		✓		✓	✓
Collected systolic and diastolic blood pressure		✓			
Excluded participants who indicated they were pregnant/breast-feeding or who were told they were allergic to lovastatin		✓			
Collected eligibility assessment on participants who did not purchase or requested assistance at the first visit; discontinued early; or completed the study		✓		✓	✓
Participants who purchased study drug provided written consent		✓			
Administered MEDFICTS dietary assessment questionnaire		✓			✓
Participants were dispensed drug and study information card		✓		✓	
Consulted with personal or study physician			✓		
Participants/users may have called product specialist (IVRS) or visited the website			✓		
Participants/users may have purchased a home cholesterol test via mail or purchased a “referral kit” to have their cholesterol tested at a local participating lab			✓		
Collected returned drug packaging and tablets					✓
Recorded new medical conditions and new prescription medications				✓	✓
Recorded adverse experiences				✓	✓
If new condition or medication was present, asked user if she/he consulted with personal or study physician regarding continued use of MEVACOR™ OTC				✓	✓
If follow-up cholesterol test not done at site, asked users if they received a test outside of the site and if they consulted with a physician regarding results				✓	✓
Users asked if their eating and exercise habits changed					✓
Users were compensated for time and travel expenses					✓
End of study questionnaires					✓

* Between visits included consumer behavior outside the study site; ** All follow-up visits were optional.

Initial Storefront Visit

Participants were given a brief, general explanation of the self-selection and purchase part of the study. Using a standardized Introductory Script, participants were told to imagine they were in an actual pharmacy, and to do what they would normally do if they came across the MEVACOR™ OTC product display while shopping in the pharmacy.

Participants were asked to make a decision about purchasing study drug, and were able to purchase 1 to 4 cartons (45-day supply per carton) of study drug (lovastatin 20 mg). Enrollment was to be stopped when about 1000 subjects had purchased drug in order to achieve the planned sample size of 1000 Users. Only the initial visit to the study site and the final visit were scheduled. Purchasers were informed that they could return to the storefront at any time during the 26-week period to purchase additional medication or a cholesterol test.

A MEVACOR™ OTC Self-Management System (SMS) was available to guide consumer behavior. This system included shelf display signage, product carton and bottle, package insert, a Quick Start Guide and brochure, video, product website, toll-free call center, and cholesterol testing referral service. A Consumer Assistance Program, which is a component of the MEVACOR™ OTC Self-Management System, provided compliance and appropriate de-selection support for participants/users choosing to enroll. This program consisted of postcard reminders, e-mails, and newsletters. Participants were offered the opportunity to enroll through the toll free phone number, the website, or with the pharmacist at the study site.

All participants had the opportunity to read the proposed outer carton label or interact with the in-store materials (e.g., shelf display), and indicate if they were interested in purchasing a carton of 45 tablets (which included support materials) for $15 (i.e., yes, no, or need more information before purchasing). Participants were allowed to purchase a total of 4 cartons (a total of 180 tablets) during the study either as single or multiple carton purchases. The initial payment was made prior to obtaining informed consent. Participants who indicated that they were not interested in an initial purchase or a repurchase during the study were asked the reason(s) why, completed an eligibility assessment (if not already done), and discontinued from the study.

To determine the reading ability of all participants, the Rapid Estimate of Adult Literacy in Medicine (REALM) test was completed during the initial storefront visit.

If participants needed cholesterol values and asked about the Cholesterol Testing sign in the storefront, they were allowed to purchase a test for $10. Although fasting for 9 to 12 hours before the test was recommended, it was not required. If participants had not fasted prior to their appointment, they were allowed to return to the site at a later date to receive the test. All participants who took advantage of cholesterol testing at the study site were asked to sign an abbreviated consent form for a pre-purchase cholesterol test. The test was a fingerstick lipid profile using the Cholestech L·D·X™ (Cholestech Corporation) desktop analyzer.

Comments:
The study design was not reflective of the naturalistic environment. The availability of a cholesterol screening test and a nurse investigator to assist at the time of purchase is not reflective of the current marketplace in the U.S.

Participants of the study could only purchase four cartons during entire study, which is not reflective of naturalistic OTC access to medications.

At the first site visit, prospective users who had not purchased a cholesterol test prior to making a purchase decision were given a cholesterol test. However, since this test was not purchased, they were not given their values or told their cholesterol was being measured. This test was performed after full informed consent was obtained, so ultimately, all Users had a First Visit cholesterol test. All users received a complimentary test at the final visit which they were not told about until they received a reminder call ~1 week before their scheduled visit. Cholesterol results from the first and last visits were used to evaluate compliance during the 26-Week study. For all cholesterol tests, the investigator recorded whether or not the participant fasted for 9 to 12 hours.

Participants had their ALT measured when the cholesterol test was given. ALT was also measured using a fingerstick test. Participants with an ALT value of > 3 x ULN were excluded. If ALT was > 3 x ULN, the participant was asked to return to the site in ~2 weeks for a follow-up test. If ALT remained > 3 x ULN, the participant was given a letter to take to his/her personal physician. The study physician followed up with the participant until resolution.

Information regarding these options was available via the website and on the toll-free number. Participants who enrolled in the Consumer Assistance Program were also mailed information on these options.

The nurse-investigators were allowed to function as pharmacists, and could answer questions initiated by the participant relating to the study or study drug. If participants requested assistance in determining if the product was right for them, the investigator completed the eligibility assessment. If participants had questions about results of their 6-week follow-up cholesterol test, the investigator directed them to the shelf signage for guidance about the 6-week test and what to do if LDL-C goal was not achieved. If there were questions which the investigator could not answer, the participant was advised to call the study physician, in order to simulate the physician consultation urged by the MOTC SMS.

Comment:
The ready access to health care professionals in the study environment may not be replicable in the OTC marketplace environment.

A study Information Card was provided at purchase. It included the days/times when the study site was open; the study site phone number to report side effects; the toll-free telephone number to consult with the study physician (to ask questions or for after hour emergencies); information needed to access the MEVACOR™ OTC website; and space for the user to write the date of first

dose of study medication. Participants/users were asked to return this card at their next visit. A new Study Information Card was given at each visit; there was a different card for follow-up visits which did not capture the first dose.

Comment:
It is unclear if or how the sponsor could provide the expansive support system (offered to study participants) to the true OTC consumer if Mevacor was switched from Rx to OTC. If the system were not available, then the ability of the study results to predict true OTC behavior is limited.

Participants could also have chosen to consult with their personal physician or, likewise, the study personnel to initially determine if MEVACOR™ OTC was right for them. Following purchase, all study related procedural questions were to be directed to the study physician or study personnel.

Prior to receiving study medication and to being assigned an allocation number (AN), participants who purchased MEVACOR™ OTC provided written informed consent. Participants who purchased MEVACOR™ OTC were asked the first 2 exclusion questions. Those who met either of the exclusion criteria were given the eligibility assessment and were discontinued from the study.

Following consent at the first site visit, all purchasers had their sitting blood pressure measured. One reading for systolic and diastolic blood pressure was recorded on a worksheet.

The nurse-investigator explained that a study physician was available in lieu of a personal physician at a toll-free number (1-800-MEVACOR), for participant/user-initiated telephone consultation. The informed consent form also reminded users to contact the study physician for medical questions and after-hour emergencies.

The MEDFICTS dietary assessment questionnaire was administered only to those who decided to purchase.

At the time of study drug purchase, an appointment for the final visit (Week 26) was scheduled.

<u>Pre-Purchase Unscheduled Visit</u>
A participant may have wanted to consult a personal physician, obtain a new cholesterol test, fast, or obtain test values on file at their physician's office prior to making a purchase decision. These participants were allowed to leave the study site (one time only) and return once the information was obtained to make a repeat purchase decision. If the participants did not return to the site (or schedule another appointment) within 2 weeks, the investigator called them to ask if they were continuing in the study. If the participants did not want to continue, the investigator administered the eligibility assessment over the phone if it had not already been collected, and compensated the participant for time required to complete the phone interview.

Between Visits
All users who were deemed eligible according to label criteria for MEVACOR™ OTC via website, IVRS or outbound call were invited to enroll in the Consumer Assistance Program. Users who were found to be ineligible were not allowed to enroll in the program. They were advised to stop taking study medication and return their unused drug and packaging to the storefront site where they were given a full refund and completed the end-of-study procedures.

Users received incentives for joining the Consumer Assistance Program. For this study, incentives included a coupon for a complementary bottle of MEVACOR™ OTC to be redeemed at their next visit to the study site, a coupon for $5 off a cholesterol test, an "American Heart Association" cookbook, and newsletters about cholesterol and healthy living reminders. In addition, participants always had the option of consulting the study physician to determine if MEVACOR™ OTC was right for them.

As a tool to confirm correct self-selection, and to direct those who made an incorrect initial use decision to discontinue, participants/users who called 1-800- MEVACOR™ to join the Consumer Assistance Program were administered the eligibility assessment (eligibility/ineligibility criteria per label), if not previously completed at the study site. Likewise, anyone who used the website to join completed the eligibility assessment on the website. Participants/users who mailed the business reply card to join were contacted by a product specialist to complete the eligibility assessment.

Post-Purchase Unscheduled Visits
Users returned to the storefront at their own initiative when they needed to purchase additional supplies of study medication or to purchase a follow-up cholesterol test. For regulatory compliance purposes, each purchaser received a study-specific bag to keep all empty/unused drug supplies and study materials and was instructed to return the bag at the final visit.

At each follow-up visit, users who returned their drug supplies bag were instructed to keep the bag (with all supplies) and return it at the final follow-up visit at which time worksheets were completed:

- Users were asked, if they experienced any discomfort since the last visit.
- Information on new prescription medications and adverse experiences (including new medical conditions) was collected. Serious adverse experiences were reported to the study physician at the toll-free physician service.
- Any users who were prescribed a new medication or developed a new medical condition were asked if a physician was consulted about continued use of MEVACOR™ OTC.

The nurse-investigator contacted all users who had purchased only 1 box and had not returned to the storefront for follow-up by Week 12, to ask if they were still participating in the study.

Users also returned to the storefront when they needed to purchase a follow-up cholesterol test. For follow-up cholesterol testing, there were 3 additional options. Participants could have:

- received a $10 test at a local participating laboratory (via referral from the study site),

- mailed a business reply card with a $10 check to receive a home test kit, or
- received a test through their doctor's office or elsewhere.

Users who did not purchase a follow-up cholesterol test at the study site were asked if they received a cholesterol test elsewhere. Results from the follow-up test and where it was performed were recorded. Users were also asked if a physician was contacted regarding any follow-up cholesterol results.

Final Visit

At the user's last follow-up visit, the nurse-investigator:
(1) administered the MEDFICTS dietary assessment questionnaire,
(2) performed an ALT and cholesterol test,
(3) asked about any change in eating and exercise habits during the study,
(4) administered the End of Study questionnaires, and
(5) provided compensation (for time and travel expenses).

If a user had not returned for the Week 26 visit, the nurse-investigator immediately attempted contact to emphasize the importance of a return visit. If the user refused to return to the study site, she/he was asked the reason why and a mailer was sent for return of all study-related materials including study medication. During this telephone contact, the nurse-investigator administered the eligibility assessment (if not previously obtained), queried the user about new prescription medications, new medical conditions, adverse experiences, and if appropriate, administered the reasons for inappropriate self-selection/de-selection portion of the End of Study questionnaire. The user was compensated for the time required to complete the phone interview.

The End-of-Study Scenario Test was administered at the last visit (Week 26) or at any point when the user decided not to repurchase. The questions covered such categories as diagnostic material use, de-selection scenarios, and reasons for inappropriate self-selection and de-selection.

At the last visit to the study site participants were given the opportunity to read and sign an IRB-approved "Permission Form for Post-Study Contact." The post-study follow-up questions were comprised of the two groupings described below.

1. Post CUSTOM Study Clarification Questions

The subgroups identified were users of MEVACOR™ OTC who, as part of the eligibility assessment, reported previous muscle pain from cholesterol-lowering medicine, concomitant use of prescription lipid-lowering medication with MEVACOR™ OTC, or current liver disease, and had not consulted with a physician prior to use of MEVACOR™ OTC. A study coordinator contacted the identified individuals and collected the follow-up question data.

2. Post-CUSTOM Survey

The Post-CUSTOM (telephone) Survey was intended to include a substantial portion of all product users who signed the permission form (~400). The objective was to obtain a more complete characterization of the users, how users interacted with the drug package and internal materials, and how the MEVACOR™ OTC Self-Management System impacted their attitudes

and behaviors with regard to cholesterol lowering and heart health. The survey commenced three months after the last participant finished in CUSTOM. For many, six months or more could have elapsed between the time that they completed or discontinued from CUSTOM and the survey.

Efficacy Measurements
Lipid measurements (total, HDL, LDL, and triglycerides) were collected at the first and last visits. The baseline and final LDL values were used to assess compliance and lipid lowering efficacy at Week 26.

For participants who obtained a lipid measurement at the Week 6 time interval (defined by the range of Weeks 4-12), this measurement was used to evaluate whether or not the user reached goal of LDL-C < 130 mg/dL.

Safety Assessment
Clinical adverse experience information was collected at all follow-up visits by asking the user if they experienced any discomfort since the last visit.

Serious adverse experiences were reported to the study physician at the 1-800- MEVACOR™ toll-free physician service.

6.1.4 Efficacy Findings

Subject Disposition
There were a total of 18692 calls to the Call Center from December 2002 through March 15, 2003 (end of the appointment-scheduling phase of the study). There were 11252 calls by unique participants who provided at least some of demographic data in the Merck database. Of these callers, 3346 participants came to the study site. The other 7906 participants were excluded prior to visiting the study site for these reasons:

- 377 did not meet eligibility criteria
- 2372 were lost to follow-up
- 4 participants were inadvertently assigned two baseline numbers
- 5153 callers were uncooperative (refused to complete the telephone interview, hang ups, inquiries, prank calls, cancelled appointments)

Of the 3346 subjects that came to the study site, 30 left the site without making a purchase decision. Table 3 depicts the number of unique calls received, assigned to each site by the callers zip code, and the purchase decision participants made during their appointment.

Table 3. Number of Participants by Study Site

Site No. and Name	Calls N (%)	Appointm. Kept N (%)	Made a Purchase Decision				No Purchase Decision N (%)
			Purchaser			Non-Purchaser N (%)	
			User N (%)	Non-User N (%)	Unknown N (%)		
1. Springfield	642 (5.7)	115 (3.4)	48 (4.5)	2 (2.1)	3 (6.0)	62 (2.9)	0 (0.0)
2. Fairfax	924 (8.2)	165 (4.9)	61 (5.7)	10 (10.6)	7 (14.0)	85 (4.0)	2 (6.7)
3. Dallas	964 (8.6)	285 (8.5)	122 (11.5)	8 (8.5)	2 (4.0)	150 (7.1)	3 (10.0)
4. Fort Worth	882 (7.8)	264 (7.9)	123 (11.6)	6 (6.4)	4 (8.0)	129 (6.1)	2 (6.7)
5. Westheimer	847 (7.5)	289 (8.6)	83 (7.8)	7 (7.4)	3 (6.0)	195 (9.2)	1 (3.3)
6. Inwood Forest	953 (8.5)	294 (8.8)	77 (7.3)	8 (8.5)	2 (4.0)	206 (9.8)	1 (3.3)
7. Willoughby	508 (4.5)	132 (3.9)	47 (4.4)	2 (2.1)	1 (2.0)	80 (3.8)	2 (6.7)
8. Brunswick	734 (6.5)	159 (4.8)	52 (4.9)	4 (4.3)	3 (6.0)	100 (4.7)	0 (0.0)
9. Pontiac	1068 (9.5)	386 (11.5)	47 (4.4)	2 (2.1)	5 (10.0)	325 (15.4)	7 (23.3)
10. Clinton Township	681 (6.1)	151 (4.5)	45 (4.2)	4 (4.3)	4 (8.0)	98 (4.6)	0 (0.0)
11. Bloomington	716 (6.4)	303 (9.1)	85 (8.0)	12 (12.8)	2 (4.0)	198 (9.4)	6 (20.0)
12. Mounds View	673 (6.0)	208 (6.2)	73 (6.9)	6 (6.4)	7 (14.0)	121 (5.7)	1 (3.3)
13. Phoenix	711 (6.3)	250 (7.5)	81 (7.6)	7 (7.4)	1 (2.0)	159 (7.5)	2 (6.7)
14. Glendale	949 (8.4)	345 (10.3)	117 (11.0)	16 (17.0)	6 (12.0)	203 (9.6)	3 (10.0)
Total	11252	3346	1061	94	50	2111	30

The Pontiac, Michigan site (Site Number 9) received the largest proportion of calls and appointments kept, and also had the largest proportion of Non-Purchasers and participants not making a purchase decision. According to the sponsor, this was a result of a unique situation that developed in this study site region, where a church located across the street from a half-way house posted unauthorized signs indicating that anyone could call the toll-free study appointment line and would receive monetary compensation for visiting the study site. According to the sponsor, a large number of individuals who had no intention of purchasing study drug were motivated to visit the study site solely to obtain the monetary compensation.

Participant disposition is summarized in Table 4. Of the 3316 participants who made a purchase decision, 1205 (36.3%) made a decision to purchase. A total of 94 purchasers did not use the product either because they were not dispensed drug (30) at the end of the visit or they returned the drug before using it (64). The two most common reasons participants returned drug before using it were that they were advised not to use it by their doctor (n=26) or they learned MEVACOR OTC was not appropriate for them (n=17). Three of these Purchaser Non-Users had elevated ALT values > 3x ULN (ALT Values: 135, 154, and 189 IU/L) and were excluded from the study and not dispensed drug. Fifty of the 1205 purchasers were lost to follow-up and their decision to use drug is unknown. The remaining 1061 purchasers are known to have used the drug.

Comments:
In the initial submission, the sponsor stated that there were 58 subjects among the 1205 purchasers with elevated ALT values greater than the upper limit of normal, but ≤ 3 x ULN who purchased but did not use the drug. Upon further request by the FDA to clarify the behavior of these subjects (why they did not use the study drug), the sponsor stated that the original report had an error in describing the data. In the subsequent amendment to the NDA submitted on December 2, 2004, the sponsor corrected the error and stated that 58 of the 1205 Purchasers

had a baseline ALT value in the > 1 x ULN to ≤ 3 x ULN range. Most of them (49 of 58) were Users, 3 were among the 50 in the Unknown Use subset, and only 6 were Purchaser Non-Users. Of the 6 Purchaser Non-Users who had a baseline ALT value in the > 1 x ULN to ≤ 3 x ULN range, 5 left the study site with drug and 1 did not. The reasons why these 6 subjects did not take Mevacor OTC are as follows: one reached cholesterol goal, two were advised by a doctor not to continue, two did not give a reason, and one learned that MOTC is not right for him.

Users were considered to have completed the study if they took at least one dose of drug, and completed all final study visit procedures. Two-thirds (66.1%) of the Users (701/1061) completed the study, and 398 Users responded to the post-CUSTOM Survey.

Table 4. Participant Disposition

Efficacy Populations	**Counts (%)**
Purchasers	1205 (36.3)
• Use Decision: Non-User	94 (7.7)
Not dispensed drug	30 (31.9)
Ineligible	8 (26.7)
ALT > 3 x ULN	3 (37.5)
Other	5 (62.5)
Withdrew consent	2 (6.7)
Refused therapy	3 (10.0)
Moved	2 (6.7)
Trial enrollment closed at site	5 (16.7)
Complete not continuing	10 (33.3)
Returned drug before using	64 (68.1)
• User Decision: User	1061 (88.0)
Completed Study*	701 (66.1)
Discontinued Study	360 (33.9)
Adverse clinical experience	108 (30.0)
Deviation from protocol occurred	2 (0.6)
Patient was lost to follow-up	13 (3.6)
Patient moved	18 (5.0)
Patient withdrew consent	157 (43.6)
Patient discontinued for other reason	53 (14.7)
Uncooperative	9 (2.5)
• User Decision: Unknown (Lost to follow-up)	50 (4.1)
Non-purchasers	2111 (63.7)
• Did not want to buy	1673 (79.3)
• Needed more info	438 (10.7)
Total who made a purchase decision	3316

* Includes participants who made decision to purchase, received and used the drug, and completed all final study visit procedures.

There were 2111 participants who did not purchase MOTC. The Non-Purchasers were composed of participants who either indicated they did not want to buy (1673) or needed more information and were considered Non-Purchasers by default (438).

There were 1061 participants who initially decided to use the product (Users). Two Users were identified as protocol violators: one subject was a physician, and the second participant took his

wife's medication before visiting and signing consent. Therefore, they were excluded and the sponsor considered the remaining 1059 as the population of Users for all summaries and analyses except for analyses pertaining to adverse experiences. The original population of 1061 is considered the population of Users for adverse experiences. Purchasers who did not use any Mevacor (Non-Users) were not included in the evaluation of the primary hypotheses. Participants who purchased drug and were lost to follow-up (Unknowns) were not considered in the evaluation of the hypotheses.

Reasons Purchasers Needed Information in Addition to the Label Instructions

The reasons purchasers and non-purchasers needed more information are listed in Table 5. The majority 826/1205 purchasers needed more information. The most common reason among purchasers needing more information was to obtain their cholesterol numbers (37.0%, 446/1205). The second most common reason was related to information such as the cost, study duration or general product information (32.0%, 386/1205). Non-Purchasers commonly cited a need for personal health information (62.5%, 1319/2111) or to talk to a doctor (46.2%, 975/2111).

Table 5. Prevalence of Specific Reasons for Participants Who Needed More Information

	Purchasers (N)	Non-Purchasers (N)	Total (N)
Did not need more information	379	10	389
Reasons for Participants Who Needed More* Information	826	2101	2927
• Study related information	386	546	932
• General information on side effect	285	377	662
• Personal health information	188	1319	1507
• To obtain cholesterol numbers	446	847	1293
• To talk to a doctor	261	975	1236
• Other information	10	95	105
Total	1205	2111	3316

* Some participants gave more than one reason for needing more information.

Comment:
The vast majority of purchasers (826/1205) and non-purchasers (2101/2111) needed more information than the label alone provided. This underscores the need for health care provider involvement in the self-selection process.

Missing Data for the Endpoint Assessment

In total, 92 of the 1059 Users had some unknown data; only 3 Users had unknown data at all three time points relevant to the study primary hypotheses (initial self-selection, de-selection through Week-6, and de-selection through Week-26). Due to missing responses the population of Users is further reduced from 1059 for the self-selection decisions and the two de-selection decision intervals:

Decision Time Point	# of Users with Complete Data	# of Users with Missing Data
Self-Selection	1037	22
De-selection through Week 6	990	69

De-selection through Week 26	986	73

Demographic and Other Baseline Characteristics

The participants' baseline characteristics are summarized in Table 6. (Appendix II). Of the 11,252 consumers who called in response to study advertising, 20.4% were Black and 5.6% were Hispanic. As shown in Table 6 the percentages of MEVACOR™ OTC Users who were Black and Hispanic were 8.5% and 5.5%, respectively.

Among the 1061 subjects who purchased and used the study drug, 430 (40.5%) were females and 631 (59.5%) were males. Of the 430 women, 161 (37.4%) were less than 55 years of age (below the targeted age):

- 23 (5.4%) women < 40 years
- 24 (5.6%) women 40-44 years
- 45(10.5%) women 45-49 years
- 69 (16.1%) women 50-54 years

The data show that a significant proportion of African Americans, compared to Caucasians, called the call center but decided not to use the drug. Of the 2298 African Americans, 632 (27.5%) showed up at the enrollment site and only 90 (3.9%) purchased and used the drug. Out of a total of 7674 Caucasian callers 2393 (31.8%) came to the enrollment site and 869 (11.3%) purchased and used the drug.

A low literacy population comprised 12.8% of all Users.

Comment:
Mevacor is a pregnancy Category X drug. The fact that a high percentage of women of child bearing age chose to use Mevacor is an important safety concern.

Correct Self-Selection According to Label Criteria

For the purposes of this discussion, self-selection refers to the decision to use the product at the initial visit. This analysis includes only purchasers of the product. It is not entirely clear from the design of the protocol that non-purchasers made a selection decision (based on the eligibility criteria). According to the proposed label, there are 4 conditions that determine correctness of the self-selection. The order that consumers had to go through in their thought process when looking at the label is as follows:

1. Age: **only** for men 45 years or older or women 55 years or older,
   plus
2. LDL-C level **only** between 130 and 170 mg/dL,
   plus
3. One or more of the following risk factors for CHD:
   Smoking
   High blood pressure
   Family history of CHD
   HDL-C 1 to 39 mg/dL

plus

4. Absence of conditions that may put the user at increased risk of an adverse experience (liver disease, high triglycerides, history of statin induced muscle pain).

The number of study participants fitting these criteria is low: only 110 (10%) out of the 1059 Users. The majority of these (N = 77) were men. Only 33 of the women Users in the study met these criteria.

Out of the 430 women who purchased and used the study drug, 269 met the age criteria (≥ 55 years), of those 100 had baseline LDL-C between 130 and 170 mg/dL, and 69 had one or more risk factors for CHD.

Male Users were older and had a higher number of risk factors for CHD. Out of the 629 male Users, 530 met the age criteria (≥ 45 years), of those 181 had baseline LDL-C between 130 and 170 mg/dL, and 137 had one or more CHD risk factor.

If we exclude 3 subjects with underlying liver disease (1 man and 2 women) and 18 (11 men and 7 women) subjects with a history of muscle weakness from taking statin, the numbers are 60 women and 125 men. There were 16 out of 60 women and 6 out of 125 men, who had only one risk factor for CHD in addition to the age and a high level (> 60 mg/dL) of HDL-C. According to NCEP guidelines, HDL-C above 60 mg/dL is a "negative" risk factor for CHD, i.e., one other factor can be negated by a high HDL-C level, and therefore, these 22 Users are not in the target population for Mevacor OTC therapy. Finally, there were 53 Users (11 women and 42 men) with a high triglyceride levels (> 200 mg/dL). The final numbers of correct self-selectors according to the strict label eligibility criteria becomes 33 women and 77 men. It is unclear which of them consulted a physician prior to the use of Mevacor. The flow chart (Figure 6) below gives a summary of the self-selection according to the proposed OTC label data.

Figure 6. Correctness of the Self-Selection

Total Users (N=**1059**: 430 women and 629 men)

↓	→	Did not meet age criteria:
Met age criteria		161 women
269 women (≥ 55 years)		99 men
530 men (≥ 45 years)		
↓	→	LDL-C not within 130-170 mg/dL
LDL-C within 130-170 mg/dL		169 women
100 women		349 men
181 men		
↓	→	≤ 1 risk factor for CHD
> 1 risk factor for CHD		31 women
69 women		42 men
137 men		
↓	→	+ liver disease
No Liver disease		2 women

67 women		1 man
136 men		
↓	→	+ history of muscle weakness
No history of muscle weakness		7 women
60 women		11 men
125 men		
↓	→	1 CHD risk factor and HDL-C > 60 mg/dL
HDL-C < 60 mg/dL		16 women
44 women		6 men
119 men		
↓	→	TG ≥ 200 mg/dL
TG < 200 mg/dL		11 women
33 women		42 men
77 men		

The specific label criteria which determined a participant's eligibility are listed in Table 7 (Appendix III). The main differences between the purchasers with a known use decision and the non-purchasers is that purchasers appeared more likely to know their cholesterol numbers (LDL, HDL and triglycerides) and meet the age guideline and less likely to have LDL-C that was too low.

Additional Analysis Conducted by the Sponsor

The sponsor conducted additional analysis that included:

- Calculated 10-year risk for myocardial infarction or coronary death;
- Off label risk subset: high lipids subset, preexisting atherosclerotic cardiovascular disease or diabetes, contraindicated underlying conditions (e.g., allergy to lovastatin).

Off Label Risk Subsets

The sponsor analyzed Self-Selection decisions by several off label subsets. These off label subsets either had a greater potential CHD risk or greater potential risk for adverse experiences:

- High lipids subset: comprised of individuals who have LDL > 170 mg/dL or triglycerides ≥ 200 mg/dL.
- Medically indicated subset: participants for whom pharmacologic lipid lowering treatment is medically indicated but for whom self-medication with lovastatin 20 mg is not appropriate. This group consisted of individuals with preexisting atherosclerotic cardiovascular disease (stroke, CHD) or diabetes.
- Contraindicated subset: individuals with contraindications, such as liver disease, pregnancy or breast-feeding, allergy to lovastatin, interacting medications, or muscle pain while previously taking a cholesterol lowering medication.

The inclusion of participants into one of the three pre-defined off label risk subsets is displayed in Table 8. Table 9 summarizes the data in Table 8.

Table 8. Purchase and Use Decision by Off Label Risk Subset Inclusion

Risk Subset Inclusion Status			Purchase Decision					
			Purchaser					
			User					
High Lipids	Medically Indicated but not OTC Appropriate	Contraindicated	N*	N**	Non-User	Unknown	Non-Purchaser	Total
No	No	No	265	184	323	3	731	1215
No	No	Yes	23	22	3	0	126	174
No	Yes	No	31	59	3	1	165	259
Yes	No	No	223	107	24	3	414	771
No	Yes	Yes	8	9	4	0	72	93
Yes	Yes	No	25	16	6	2	78	127
Yes	No	Yes	26	16	10	1	101	154
Yes	Yes	Yes	7	9	0	0	54	70
No	Yes	Unknown	0	2	0	1	8	11
Yes	No	Unknown	3	1	0	0	13	17
Yes	Yes	Unknown	1	1	0	0	4	6
Yes	Unknown	No	0	0	0	1	0	1
Yes	Unknown	Yes	0	0	0	0	0	0
No	Unknown	Yes	0	0	0	0	0	0
Unknown	No	Yes	0	0	0	0	5	5
Unknown	Yes	No	0	0	0	0	2	2
Unknown	Yes	Yes	0	0	0	0	1	1
Unknown	Yes	Unknown	0	0	0	0	1	1
Unknown	Unknown	Yes	0	0	0	0	1	1
Yes	Unknown	Unknown	0	0	0	0	0	0
No	No	Unknown	3	4	2	0	26	35
No	Unknown	No	0	0	0	0	1	1
Unknown	No	No	1	0	0	0	5	6
No	Unknown	Unknown	0	0	0	0	3	3
Unknown	No	Unknown	0	0	0	0	0	0
Unknown	Unknown	No	0	0	0	0	0	0
Unknown	Unknown	Unknown	15	0	10	38	300	363
Total			631	430	94	50	2111	3316

* Without physician override; ** With physician override.

Table 9. Purchase and Use Decision by Off Label Risk Subset Inclusion

	Purchase Decision				
	Purchaser				
Risk Subset Inclusion Status	User (N=1061)	Non-User (N=94)	Unknown (N=50)	Non-Purchaser (N=2111)	Total (N=3316)
Not included in any risk subset	449 (37.0)	32 (2.6)	3 (0.2)	731 (60.2)	1215 (100%)
Included in at least one risk subset	589 (34.8)	50 (3.0)	9 (0.5)	1045 (61.7)	1693 (100%)
Unknown	23 (5.6)	12 (2.9)	38 (9.3)	335 (82.1)	408 (100%)

Table 10 displays the specific reasons why participants were classified into the off label risk subsets.

Table 10. Prevalence of Specific Reasons for Categorizing Participants in the Off Label Risk Subsets

Risk conditions*	Purchase Decision					Total (N=3316) n
	Purchaser				Non-Purchaser (N=2111) n	
	User (N=1061)		Non-User (N=94) n	Unknown (N=50) n		
	n[#]	n[¶]				
High LDL-C or TRG	281	154	40	7	664	1146
LDL-C >170 mg/dL	150	75	26	1	299	551
TRG ≥ 200 mg/dL	170	98	25	7	468	768
Potentially Interacting Drugs	12	20	4	0	116	152
Nefazodone	1	2	0	0	3	6
Cyclosporine	0	1	0	0	2	3
Erythromycin/Clarithromycin	2	1	1	0	6	10
Ketoconazole/Itraconazole	0	0	0	0	2	2
Gemfibrozil	2	8	2	0	36	48
Niacin (>1000 mg/d)	7	8	1	0	41	57
Protease Inhibitors	1	0	0	0	33	34
Other Rx lipid lowering therapy	62	103	19	1	424	609
Pregnant or breastfeeding	0	0	0	0	12	12
Current liver disease	3	6	1	0	70	80
Allergy to MEVACOR™	0	0	0	0	13	13
Previous muscle pain	53	33	13	1	200	300
Subjects with stroke, CHD or diabetes	71[†]	97	13	4	385	570
Stroke	16	15	2	2	100	135
CHD	37	52	9	1	186	285
Diabetes	30	43	5	1	196	275

* Participants may have multiple contraindications. [#] Without Physician Override. [¶] With Physician Override.
[†] Includes one protocol violator.

Of the 165 subjects who were taking other prescription lipid lowering therapy, 62 did not consult a physician: 52 used lovastatin concomitantly, 9 substituted lovastatin for their current lipid lowering therapy, 1 participant was a protocol violator. The sponsor states that 43 out of those 52 Users responded to the Post-CUSTOM Clarification Questions program, and 42 reported they stopped taking their Rx cholesterol-lowering medication while using Mevacor and one continued to use the Rx drug concomitantly.

Comments:
Of the 1061 Users, 589 (55.5%) had one or more risk conditions specified on the MOTC label. In addition, 23 (2.2%) subjects' self-selection status was not known due to missing information. This brings the number to only 449 (42.3%) of Users who definitely did not have risks for using MOTC 20 mg.

A significant number of Users in the study with one or more risk conditions for the use of MOTC were categorized by the sponsor as appropriate self-selectors if they mentioned a contact with a physician. The physician contact and the information discussed were not verified by the study personnel. Therefore, a failure in self-selection per the label should not be dismissed on this basis. Even if we assume that some participants, in fact, discussed a particular risk condition

with their personal physician, a significant proportion of users with each individual risk factors remain who did not get physician clearance. If we compare the categories, a listing of these non clearance users follows:

- *37.5% (62 out of 165) of Users were taking prescription lipid lowering medications without physician override (WPO),*
- *64.5% (281/435) of Users had high LDL-C or TG WPO,*
- *37.5% (12/32) of Users took potentially interacting drugs WPO,*
- *41% (30/73) had diabetes WPO,*
- *41.5% (37/89) of Users had CHD WPO,*
- *51.6% (16/31) of Users had a history of stroke WPO,*
- *61.6% (53/86) of Users had a history of previous muscle pain WPO.*

Can Consumers Self-Select Based on Their Risk for CHD Factors?

Table 11 presents the distribution of study participants by the number of CHD risk factors for several of the study populations. A higher percentage of Users had 2 or more CHD risk factors compared to the Non-Purchasers (57.3% vs. 42.8%) and were thereby statin eligible by ATP III.

Table 11. Self-Reported CHD Risk Factors

		Use Decision			
		User (N=1061)	Non-User (N=94)	Unknown (N=50)	Non-Purchaser (N=2111)
No. of CHD Risk Factors	0	93 (8.8)	9 (9.6)	16 (32.0)	398 (18.9)
	1	360 (33.9)	37 (39.4)	29 (58.0)	809 (38.3)
	2	381 (35.9)	33 (35.1)	3 (6.0)	570 (27.0)
	3	178 (16.8)	13 (13.8)	1 (2.0)	272 (12.9)
	4	46 (4.3)	2 (2.1)	1 (2.0)	58 (2.7)
	5	3 (0.3)	0 (0.0)	0 (0.0)	4 (0.2)
Age (Years)	Male: < 45	101 (16.0)	8 (15.4)	12 (35.3)	388 (31.7)
	≥ 45	530 (84.0)	44 (84.6)	22 (64.7)	837 (68.3)
	Female: < 55	161 (37.4)	15 (35.7)	7 (43.8)	502 (56.8)
	≥ 55	269 (62.6)	27 (64.3)	9 (56.3)	382 (43.2)
Smoking Status	Yes	120 (11.5)	14 (16.7)	1 (8.3)	393 (21.8)
	No	926 (88.5)	70 (83.3)	11 (91.7)	1411 (78.2)
Family History of CHD	Yes	372 (35.6)	23 (27.4)	2 (16.7)	561 (31.1)
	No	674 (64.4)	61 (72.6)	10 (83.3)	1244 (68.9)
Hypertension	Yes	349 (33.5)	25 (29.8)	3 (25.0)	519 (28.8)
	No	694 (66.5)	59 (70.2)	9 (75.0)	1285 (71.2)
HDL-C	Male: < 40 mg/dL	173 (27.9)	11 (23.9)	5 (55.6)	259 (25.5)
	≥ 40 mg/dL	289 (46.7)	19 (41.3)	2 (22.2)	366 (36.0)
	Don't know	157 (25.4)	16 (34.8)	2 (22.2)	392 (38.5)
	Female: < 40 mg/dL	42 (9.9)	6 (15.8)	0 (0.0)	66 (8.4)
	≥ 40 mg/dL	254 (59.8)	25 (65.8)	1 (33.3)	429 (54.9)
	Don't know	129 (30.4)	7 (18.4)	2 (66.7)	287 (36.7)

Comment:
According to the NCEP ATP III treatment guidelines, for people with 0 to 1 risk factor for CHD to qualify for drug therapy, their LDL-C level has to be ≥ 190 mg/dL. It is of concern that 42.7% of Users did not meet the risk factor criteria and used the product.

Calculated 10-Year Risk for Hard CHD*

Those who made a purchase decision were not required to calculate their 10-year risk score for Hard CHD to use MOTC, but the sponsor did this calculation. Across classification of the 1059 Users (excludes 2 protocol violators) by their number of self-reported CHD risk factors and their calculated 10-year risk for hard CHD (myocardial infarction and coronary death) is presented in Table 12. The sponsor states that they calculated hard CHD risk using the Framingham risk assessment tables published in the 2001 NCEP ATP III treatment guidelines. Actual measured values for total cholesterol, HDL-cholesterol, and blood pressure were used for the calculation along with the participant's self-reported values for age and smoking status.

Table 12. Calculated 10-Year Hard CHD Risk (the sponsor's calculations)

	Number of Self-Reported CHD Factors						Total
10-year Hard CHD Risk	**0**	**1**	**2**	**3**	**4**	**5**	**N (%)**
Males: Unknown	6	21	13	10	0	0	50 (7.9)
Undefined (Age > 79 Years)	0	1	4	0	0	0	5 (0.8)
< 5%	29	26	13	1	0	0	69 (11.0)
5 to <10%	0	43	42	15	2	0	102 (16.2)
10 to 20%	0	92	95	45	9	0	241 (28.3)
>20 to 25%	0	3	13	13	2	0	31 (4.9)
>25%	0	1	12	9	2	1	25 (4.0)
CHD, Diabetes or Stroke	1	15	41	32	15	2	106 (16.9)
Sub-Total	36	202	233	125	30	3	629
Female: Unknown	4	7	5	2	1	0	19 (4.4)
Undefined (Age > 79 Years)	0	1	1	1	1	0	4 (0.9)
< 5%	53	105	52	10	0	0	220 (51.2)
5 to <10%	0	25	36	17	3	0	81 (18.8)
10 to 20%	0	6	16	8	5	0	35 (8.1)
>20 to 25%	0	0	2	2	1	0	5 (1.2)
>25%	0	0	3	1	1	0	5 (1.2)
CHD, Diabetes or Stroke	0	14	32	11	4	0	61 (14.2)
Sub-Total	57	158	147	52	16	0	430
All Users: Unknown	10	28	18	12	1	0	69 (6.5)
Undefined (Age > 79 Years)	0	2	5	1	1	0	9 (0.8)
< 5%	82	131	65	11	0	0	289 (27.3)
5 to <10%	0	68	78	32	5	0	183 (17.3)
10 to 20%	0	98	111	53	14	0	276 (26.1)
>20 to 25%	0	3	15	15	3	0	36 (3.4)
>25%	0	1	15	10	3	1	30 (2.8)
CHD, Diabetes or Stroke	1	29	73	43	19	2	167 (15.8)
Total	93	360	380	177	46	3	1059

As shown in Table 12, there was a notable difference between men and women in the distribution of CHD risk. A total of 51.2% of the women had 10-year risk for hard CHD that was less than 5% compared to 11.0% of the men. In contrast, 59.5% of the men fell in the 5% to 25% range compared to 28.1% of the women falling in this range.

* Hard CHD is defined as myocardial infarction and coronary death.

According to the sponsor, by ATP III, Users with 2 or more CHD risk factors and CHD risk of ≤ 20% were eligible for therapy with MOTC. Of the 1059 Users, 606 (57%) reported having multiple (≥ 2) CHD risk factors. As defined by NCEP ATP III treatment guidelines, the sponsor states that 57% of Users, who were neither secondary prevention Users nor diabetics and whose risk could be calculated (467/814) were at intermediate risk (multiple risk factors and CHD risk ≤ 20%), 32% (281/814) were at low risk (0-1 risk factor and a 10-year risk CHD risk < 10%) and 7% (66/814) were considered as CHD risk equivalents with a 10 year CHD risk > 20%. Framingham risk scores could not be calculated for 9 Users over the age of 79 or for 69 Users with missing data. In addition, not counting the 1 high risk protocol violator, there were 70 high risk Users (secondary prevention Users with CHD or a history of stroke, or Users with diabetes mellitus) that began taking MOTC without first consulting their physician (see Table 10), and 97 of the 167 such high risk Users that consulted with their physician before taking MOTC. Thus, the majority of Users (86%) (excluding 69 Users with Unknown risk and 9 Users with Undefined risk) had a 10-year risk ≤ 20% (289+183+276) or were high risk Users (n=97, see Table 10) who had consulted with their physician prior to taking MOTC. Most low risk Users were female (65%, 183/281), whereas most intermediate risk Users were male (67%, 314/467).

Two hundred eighty-nine (27.3%) Users had a 10 year CHD risk of < 5%.

CHD, Diabetes, Stroke subset (n=167)
Table 18 shows that this subset was made up of 106 men and 61 women. Seventy (70) Users did not consult with a physician prior to using MEVACOR™ OTC. The other 97 Users in this subset consulted with a physician about MEVACOR™ OTC.

Can Consumers Self-Select Based on Their Knowledge of Their Cholesterol?
A finger stick blood evaluation was performed using a desktop analyzer for all participants choosing to purchase study drug. Table 13 presents information for both the fasted and non-fasted subgroups as well as the overall User population. The mean and median values for LDL-C were lower, and for triglycerides were higher, in the non-fasted group compared with the fasted group. The agreement between self-reported and measured LDL-C values is displayed in Table 14.

Table 13. Baseline Laboratory Measurements

		Fasted	Non-fasted	Total
Total Cholesterol (mg/dL)	# of participants (N)	414	637	1053
	Mean (S.D.)	251.8 (44.6)	243.3 (50.1)	246.7 (48.2)
	Median	252	239	243
	Range	132 to 456	103 to 501	103 to 501
LDL-C (mg/dL)	N	378	551	931
	Mean (S.D.)	167.2 (39.6)	150.4 (41.9)	157.3 (41.8)
	Median	164.5	146	155
	Range	66 to 362	10 to 295	10 to 362
HDL-C (mg/dL)	N	406	606	1014
	Mean (S.D.)	46.4 (13.4)	47.3 (13.6)	47.0 (13.5)
	Median	44	45	45
	Range	14 to 98	14 to 98	14 to 98
Triglycerides (mg/dL)	N	413	637	1052
	Mean (S.D.)	203.2 (126.4)	240.1 (141.0)	225.4 (136.5)
	Median	167	201	189
	Range	44 to 651	44 to 651	44 to 651
ALT (IU/L)	N	412	638	1054
	Mean (S.D.)	23.8 (8.7)	22.8 (9.0)	23.2 (8.9)
	Median	22	20	21
	Range	9 to 66	10 to 80	9 to 80

Table 14. Number of Users by Self-Reported and Measured LDL-C Values (Baseline)

Self-Reported LDL-C	Measured LDL-C (mg/dL)				Total
	Missing	< 130	130 to 170	> 170	
Missing	15	0	10	2	27
Unknown	66	55	103	94	318
< 130 mg/dL	10	87	16	9	122
130-170 mg/dL	19	54	250	44	367
> 170 mg/dL	18	13	26	168	225
Total	128	209	405	317	1059

For LDL-C, 667 (63%) of the user population had both a known self-reported LDL-C value and a non-missing measured LDL-C from the Cholestech L·D·X™ evaluation. Ninety-three Users over-reported (self-reported greater than measured) and 69 Users under-reported (self-reported less than measured) their LDL-C.

For Total-C, 855 of the user population had both a known self-reported Total-C value and a non-missing measured Total-C from the Cholestech L·D·X™ evaluation. A total of 663 (77.5%) of the 855 had a self-reported Total-C that agreed with the measured Total-C value. Ninety-one User (91) over-reported and 101 Users under-reported their Total-C.

Comments:
There were relatively high values of HDL-C in the study population (mean of 47 and median of 45 mg/dL). None of the Users had ALT value greater than 3 x ULN (normal range 20-40 IU/L) at baseline.

A significant number of participants in the study did not correctly identify their LDL-C level. Out of a total of 317 participants with measured high (> 170 mg/dL) LDL-C levels, 168 (53%) self reported their LDL-C level correctly, 53 (16.7%) underreported, and 96 (30%) did not know or their self-reported LDL-C levels were missing. For the other subgroups, the correct self-reporting LDL-C level rates were:

- *42% for the group with a measured LDL-C level < 130 mg/dL*
- *62% for the group with a measured LDL-C level of 130 to 170 mg/dL*

The knowledge of cholesterol levels becomes important in OTC setting, if there is no access to testing.

Duration of Use

The Users whose duration of treatment was > 24 weeks (168 days) were considered by the sponsor to have remained in the study for 26 weeks and were considered to be persistent. The sponsor determined that a total of 61.8% (656/1061) of the Users had treatment duration of at least 169 days, and considered these Users to be persistent. Data on duration of treatment are presented in the Safety Section of the review.

The sponsor acknowledges that the above assessment of persistence is confounded by several factors:

- The MEVACOR™ OTC Self-Management System contained prominent and pervasive messages encouraging appropriate discontinuation of therapy.
- Study drug stop date was not collected from Users. The date of last drug return (or last contact with the User if drug was not returned) was used as a surrogate for therapy stop date.
- Some Users "remained in the trial" until their scheduled last visit even if they had discontinued study drug long before their final visit, or had never taken any drug.

Related information on persistence is available from the Post-CUSTOM Survey. Of the 398 Users who responded to the survey, 266 reported that they "generally used" MEVACOR™ OTC throughout the 6-month study period. When these 266 Users were asked about the likelihood of their continuing with MEVACOR™ OTC had it been available after the study, 77% (205/266) responded that they would have been "very likely" to continue to use the product, and another 9% (25/266) said they would have been "somewhat likely" to continue use.

Compliance

The sponsor states that compliance was calculated as the number of tablets taken divided by the number of days users had access to medication in all 1059 Users. The percent compliance can be more than 100% for several reasons, including:

- User actually took more than 1 tablet per day
- Artifacts created by data handling and entry guidelines
- Error in data collection or entry (discovered after database lock)

Comments:
The methodology to assess compliance is imprecise because diaries on drug use were not given to participants. In addition, participants were not asked if they were taking MEVACOR OTC daily, and when they stopped taking the study drug. Rather the duration of treatment was estimated based on the time participants had the drug in their possession, which overestimates the drug exposure. This issue is highlighted by the one subject who died while participating in the study. Since the study medication was not returned to the study personnel immediately, he was considered to be on drug therapy for 9 days after his death.

The sponsor states that the data support the conclusion that there is no evidence of excessive dosing on a chronic basis in the User population. However, consumers were restricted to purchasing no more than 4 cartons of Mevacor during the study. The data collection methods and restriction on purchasing do not allow a meaningful assessment of "excessive dosing."

Effectiveness of the MEVACOR™ OTC Self-Management System in Guiding Appropriate Behavior

The sponsor submitted a plan for a self-management system program to help consumers use Mevacor OTC properly. The main part of this program that was evaluated was the physician override of label criteria. It is important to note in the actual use study that consumers would have had to leave from their initial visit to consult with their physician and then return for an unscheduled visit. Even though there were a high number of reported "physician overrides," there were few unscheduled visits. The sponsor provided the following explanation for this discrepancy: physician consultations reported at the pre-purchase unscheduled site visit as well as consultations reported to have taken place after product purchase (either during the study or at the last visit) but before first use were both considered to be physician overrides (refer to page 20).

Analyses of Self-Selection

The study results show that none of the pre-specified primary hypotheses were met. These data are summarized in Table 15 and Table 16. Table 15 depicts the data using MASM (AL and AB) or MUSM (NAB and NAS) classifications. Table 16 provides the cumulative frequencies (AL through NAB) and the number of unknowns at each time interval.

Table 15. Assessment of Participant Behavior by Decision Time Interval (Users)

	MASM			MUSM		
Decision	AL	AB	Total	NAB	NAS	Total
Self-Selection	484	87	571	357	109	466
De-Selection through Week 6	366	43	409	483	98	581
De-Selection through Week 26	348	146	494	391	101	492

AL=According to label; AB=Adequate benefit; NAB=Not adequate benefit; NAS=Not adequate safety; MASM=Medically acceptable for self-management; MUSM=Medically unacceptable for self-management.

Table 16. Cumulative Frequency of Participant Behavior by Decision Time Point (Users)

Decision	Cumulative Frequency			NAS	Unknown	Total*
	AL	AL+AB	AL+AB+NAB			
Self-Selection	484 (45.7%)	571 (55.1%)	928 (87.6%)	109 (10.3%)	22 (2.1%)	1059
De-Selection through Week 6	366 (34.6%)	409 (41.3%)	892 (84.2%)	98 (9.3%)	69 (6.5%)	1059
De-Selection through Week 26	348 (32.9%)	494 (50.1%)	885 (83.6%)	101 (9.5%)	73 (6.9%)	1059

*Total=AL+AB+NAB+NAS+Unknown

Around 10% of User behavior was classified as MUSM-NAS at each interval.

Comment:
On the primary hypotheses, the sponsor estimated ≥ 80% of subjects will make correct self-selection decision, ≥ 75% will correctly de-select by Week 6, and ≥ 75% will correctly de-select by Week 26. Results of the study show that those percentages were 55.1%, 41.3%, and 50.1%, respectively. The majority of participants in the sponsor's correct self-selection and de-selection groups were those who were assessed as correct decision makers because of "physician override."

Additional (post-hoc) Analyses of Self-Selection (Sponsor's)
Since the Data Analysis Plan (DAP) approach yielded results that did not meet the hypothesized benchmarks, the sponsor decided to use an alternative approach (Complementary Assessment of Benefit and Safety or CABS approach) to assess whether or not off-label behavior, occurring in the context of the individual consumer, can also provide a reasonable degree of benefit without compromising optimal safety.

The sponsor states that under the set of rules defined in the DAP, a study participant's ability to derive benefit was ignored if that participant had one or more of the specific conditions or situations identified in the label ineligibility criteria and used the product without first consulting with a physician. Therefore, the sponsor reanalyzed the initial use decision and introduced an additional category of correctness of initial use decision, called "closely adhered to label benefit criteria". This is defined as individuals who deviated from label defined ranges for age, LDL-C, HDL-C or number of CHD risk factors but who:

- knew their complete lipid profile (LDL-C, HDL-C and triglycerides)
- had a self-reported triglyceride < 200 mg/dL
- did not substitute MEVACOR™ OTC for an prescription cholesterol lowering medication, and
- did not have diabetes, heart disease, or stroke

Comment:
It appears that for the "closely adhered" category, if a person knew his/her lipid profile, the actual numbers did not matter.

Table 17 presents the initial decision to use MEVACOR™ OTC for all 1059 Users. The columns represent the original DAP-defined self-selection behavioral classification. The rows represent varying levels of adherence to the label eligibility criteria regarding benefit: adherence, close adherence, non-adherence.

Table 17. Number of Participants by Adherence to Label Benefit Criteria for Initial Use Decision

Adherence to Label Benefit Criteria	AL	AB	NAB	NAS	Unknown	Total
Adhered to label Benefit Criteria	484	0	0	1	0	485
• Without physician override	68	0	0	1	0	69
• With physician override	416	0	0	0	0	416
Closely adhered to label benefit criteria*	0	87	81	27	7	202
• Outside of age criteria	0	9	50	3	2	64
• Absence of label risk factors	0	45	47	11	3	106
• LDL-C < 130 mg/dL	0	8	4	5	1	19
• LDL-C > 170 mg/dL	0	49	31	11	4	95
• HDL-C ≥ 60 mg/dL	0	21	40	9	1	71
Did not adhere to label benefit criteria	0	0	276	81	0	357
• Did not know lipid profile	0	0	145	43	0	188
Did not know LDL-C	0	0	134	40	0	174
Did not know HDL-C	0	0	115	37	0	152
Did not know TG	0	0	116	37	0	153
• Self-reported TG ≥ 200 mg/dL	0	0	136	34	0	170
• Subs MOTC for lipid-lowering meds	0	0	10	1	0	11
• High CHD risk	0	0	38	32	0	70
Diabetes	0	0	18	12	0	30
CHD	0	0	18	18	0	36
Stroke	0	0	7	9	0	16
Missing eligibility assessment	0	0	0	0	15	15
Total	484	87	357	109	22	1059

* Participants may be counted in more than one subgroup

A total of 485 Users adhered to all of the label benefit criteria. Four hundred eighty-four (484) also had a DAP self-selection classification of According to Label (AL) implying that they had none of the specific conditions or situations identified in the label ineligibility criteria or that they consulted with a physician, plus one subject who was classified as NAS (not adequate safety) due to previous muscle pain, weakness, or tenderness from taking a cholesterol-lowering medication.

An additional 202 Users closely adhered to the label benefit criteria. The distribution of individuals in this subset by their calculated 10-year risk for hard-CHD (based on measured lipid values) was as follows:

- 4 participants had a 10-year risk for hard-CHD exceeding 20%
- 101 had a 10-year risk for hard CHD in the 5 to 20% range.
- 90 had a 10-year risk for hard CHD that was less than 5% (20 men and 70 women).

The sponsor combined users that adhered and those who closely adhered to the label benefit criteria. This analysis brought the sponsor's new number of appropriate self-selectors to a total of 686 of the 1059 Users.

A total of 357 Users did not adhere to the label benefit criteria for one or more of the following reasons:

- 188 did not know their complete lipid profile (LDL-C, HDL-C and triglycerides) when making their decision to use MEVACOR™ OTC.
- 170 had a self-reported triglyceride ≥ 200 mg/dL. This was based on a non-fasted triglyceride evaluation in 95 of the 170 individuals. The majority (125 of 170; 74%) had reported triglyceride values below 400 mg/dL, but 26% (45 of 170), had triglycerides ≥ 400 mg/dL.
- 11 indicated that they substituted MEVACOR™ OTC for a prescription cholesterol-lowering medication.
- 70 indicated that they had diabetes, heart disease, or stroke (high CHD risk subset). Forty-six (46) of the 70 did not report being on a prescription cholesterol-lowering medication and 26 of the 70 reported a physician interaction during the course of this study.

Comments:
One of the conditions for the drug to be safely used in the over-the-counter setting is appropriate self-selection based on the labeling. Data from this study show that significant number of participants did not know their lipid profile, which is the basis for the treatment of hypercholesterolemia with statins.

The most common reason for failure in self-selection was that participants did not know their cholesterol levels. A total of 188 did not know their complete lipid profile and chose to use the drug. This comprises 18% of all 1059 Users. Even though the subsequent testing showed that 175 of the 188 participants had elevated values of LDL-C or Total-C, this still does not justify their self-selection. Additionally, it is unclear from the submission how many of those participants had LDL-C levels that fell within the acceptable treatment range. Elevated triglycerides (> 200 mg/dL), one of the "do not use" conditions on the label were present in 170 participants; they comprised 16% of all Users.

The sponsor states that although 357 Users did not adhere to the label benefit criteria, at least 72% (n=258) of this cohort was eligible for statin therapy by ATP III guidelines, and thus, raising the initial appropriate self-selection rate from 55.1% to 89% (944 of 1059 users). These post-hoc analyses are not based on the subject's self-selection decision but rather on the retrospective analyses of their baseline characteristics.

There were 109 Users (Table 17) identified as making an initial decision to use MEVACOR™ OTC that potentially put them at increased risk of an adverse experience.

The specific label ineligibility criteria used to identify these 109 Users were the following:
• allergy to lovastatin

• pregnant or breast-feeding
• liver disease
• previous muscle pain, weakness or tenderness from taking a cholesterol lowering medication
• taking (or unsure if they are taking) potentially interacting medications
• concomitant use with a prescription cholesterol-lowering medication

Sixty-three (63) of the 109 completed the study, although one reported that a doctor advised him/her not to continue. Thirty (30) of the 109 discontinued from the study on or before Study Day 84 of which 23 reported either that they learned MEVACOR™ OTC was not right for them (n=17) or that a doctor advised them not to continue (n=3) or both (n=3). An additional 16 of the 109 discontinued from the study after Study Day 84 of which 6 reported either that they learned MEVACOR™ OTC was not right for them (n=5) or that a doctor advised them not to continue (n=1).

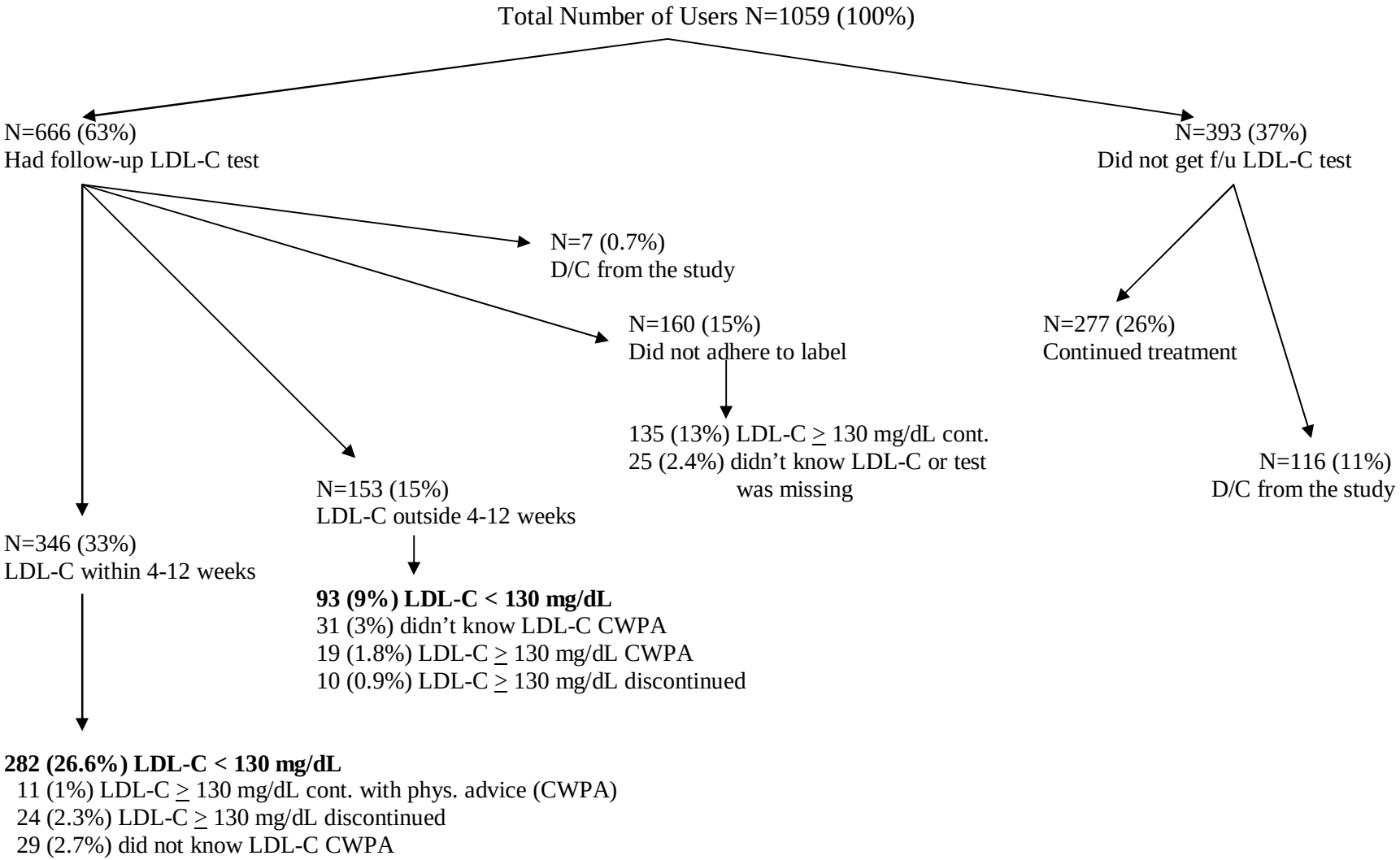
Comment:
A total of 10.3% of Users made a self-selection error to take MOTC that could put them at risk. Given the incorporated study pre-purchase screening procedures (telephone screening prior to enrollment, the availability of Cholestech analyzer, and the interactions with a study physician and a nurse investigator), the risk may increase significantly if the drug becomes available to a large unscreened OTC population of consumers.

How Many Users Obtained a Follow-Up Cholesterol Test, How Did They Use That Information and Did They Achieve Goal?
The label instructed users to test their cholesterol after 6 weeks of treatment. Table 18 (Appendix IV) presents details on the decision for continuing use of MEVACOR™ OTC with regard to follow up cholesterol testing for all 1059 Users: getting a follow-up cholesterol test within a specific time frame after starting to use MEVACOR™ OTC, and whether to continue or stop using the product based on the test results. The flow chart below (Figure 7) gives a summary of the same data.

A total of 666 (346+153+160+7, Table 18) of the 1059 Users obtained at least one follow-up cholesterol test prior to the mandatory end-of-study test. This includes 406 individuals who had one follow-up test and 260 individuals who had more than one follow-up test (up to six tests). The remaining 393 (37%) individuals did not get a follow-up cholesterol test. One hundred sixteen of the 393 discontinued from the study on or before Study Day 84. This leaves 277 (26%) individuals who did not get a follow-up cholesterol test and continued in the study past Day 84 (91 discontinued from the study after study Day 84 and 186 completed the study).

A total of 123 (11.6%) out of 1059 individuals discontinued from the study and were considered missing for the assessment of adherence to label criteria regarding the follow-up cholesterol test. This includes the 116 participants described in the preceding paragraph as well as 7 individuals who did get a follow-up cholesterol test, but who discontinued and did not report that the results of the cholesterol test were a factor in their decision. Therefore, 936 Users were available for the assessment of adherence to label criteria regarding the follow-up cholesterol test.

Figure 7. Decisions with Respect to Continuation of Therapy



Three hundred forty-six (346, 36.5%) Users obtained a follow-up cholesterol test within the pre-defined interval for Week 6 (within 4-12 weeks) and exhibited behavior that adhered to the label directions. This included 282 individuals who achieved an LDL-C goal level of < 130 mg/dL and continued with the product, 24 individuals who did not achieve the LDL-C goal level of < 130 mg/dL and discontinued use of the product and 40 individuals who continued use of the product following a physician interaction.

An additional 153 Users obtained a follow-up cholesterol test and exhibited behavior that adhered to the label directions for LDL-C goal except that the follow-up test was obtained outside of the pre-defined interval for Week 6.

Four hundred thirty-seven (437) Users exhibited behavior that did not adhere to label criteria regarding the follow-up cholesterol test. This includes the 277 Users who did not get a follow-up cholesterol test and continued in the study past Day 84 (described earlier) and 160 Users who got a follow-up cholesterol test and exhibited behavior that did not adhere to the label directions for LDL-C goal. Of the 277 Users who did not get a cholesterol test and continued without a physician override (Table 18), an end of study LDL-C value was available for 201 of these and 55% (111 of 201) achieved LDL-C target goal. One hundred-thirty (130) of the 270 provided a reason for their behavior:

- 51 indicated that it "was not convenient to get a test"
- 18 of the 64 Users who were categorized as 'other' had discontinued MOTC treatment, therefore it was unnecessary for these individuals to get a test
- 78 of the 147 Users who did not provide a reason indicated that they were not aware of the label directive

Of the 160 Users who got a follow up cholesterol test but who did not adhere to label criteria regarding that test, 135 Users had an LDL-C ≥ 130 and continued with treatment. Additionally, only 14 of 97 Users who did not provide a reason indicated that they were not aware of the label directive and the remaining 83 of 97 were not asked the question.

Comments:
Even though a physician's advise to continue or discontinue the drug therapy is a valid justification for deviation from the label use directions, this is not always possible in the over-the-counter setting. We cannot estimate the real rate of consumer contact with a health care provider during this study, because the contact itself and the information discussed with a health care provider were not verified by the study personnel. Compliance with the follow-up cholesterol testing was as follows: 666 (63%) of the 1059 Users obtained a follow-up test during the 6 months of the study. Only 346 (32.7%) obtained it within the specified time interval of 4 to 12 weeks. A total of 282 (26.6%) Users achieved the LDL-C goal of < 130 mg/dL within 4 to 12 weeks, and an additional 93 (9%) Users had their LDL-C test outside the 4 to 12 week period and achieved LDL-C goal.

For the group of 484 Users who self-selected according to the label criteria (includes physician override), 297 achieved LDL-C goal (< 130 mg/dL) at the end of the study. Thirty-nine of these 297 participants discontinued the study for various reasons. Twenty-three of these participants gave reasons that were directed by the label. These reasons were:

- *Did not reach cholesterol goal*
- *Adverse experience that was judged to be muscle pain related*
- *Doctor advised not to continue*
- *Learned MEVACOR OTC is not right for me*

Sixty-eight participants initially self-selected correctly according to the label criteria without a physician interaction. They are a subset of the above 484. Of these 68 participants, 41 achieved their LDL-C goal (< 130 mg/dL) at the end of the study. Three of these 41 participants discontinued the study for various reasons; two of these had reasons that were directed by the label. Table 19 below summarizes these data.

Table 19. Participants That Self-Selected Correctly According to Label: Goal Status & Discontinued Study Counts

	Achieved Goal at the End of the study	Discontinued Study	Discontinued Study Due to Reasons on Label
Initially self-selected Correctly According to Label (N=484)	297	39	23
Initially self-selected Correctly According to Label Without Physician Interaction (N=68)	41	3	2

Of the 398 users who responded to the Post-CUSTOM survey, 139 (35%) felt that they did not attain the LDL-C goal. Seventy-five (75) of the 139 reported that they subsequently spoke to their physician about cholesterol, and an additional 28 of the 139 said that they had made an appointment to talk with their physician. Of the 75 people who said they saw their physician, 56 were put on a new treatment plan, and prescription cholesterol-lowering medication was part of the treatment plan for 55 of the 56.

<u>User Decisions Related to Emergent Medical Conditions, New Prescription Medications, and Occurrence of Unexplained Muscle Pain</u>

Table 20 (Appendix V) presents the decision for continuing use of MEVACOR™ OTC for all 1059 Users. Three hundred sixty six (366, 35%) of the 1059 Users reported an emergent medical condition or new prescription:

- One hundred sixty-one (105+53+3) reported an emergent medical condition other then an unexplained muscle pain:
    - 6 newly diagnosed cases of diabetes,
    - 1 stroke, and
    - 4 cases of coronary artery disease.

One hundred five (105) of the 161 informed a physician about taking MEVACOR™ OTC including five of the six diabetes cases and three of the four coronary artery disease cases.

Examples of other commonly reported new medical conditions included sinus infection (13 cases), hypertension (11 cases), and urinary tract infection (8 cases).

- Two hundred seventy reported a new prescription during the period they were in the study. Only two of the 270 reported a specific interacting medication and failed to inform a physician about taking MEVACOR™ OTC. Both individuals were taking clarithromycin, one stopped study medication and the second interrupted study medication.
- Sixty-three reported unexplained muscle pain during their time in the study. Sixteen (16) of the 63 participants who reported unexplained muscle pain did not discontinue drug or inform a physician, although one did discontinue from the study at some point. Of the remaining 15, 8 provided a reason for not discontinuing or informing a physician. The reasons included two Users who said that they, in fact, did talk to a doctor and 2 who knew what was causing the problem. One individual stated that the problem stopped after a short time, one participant said the problem was minor, and 2 provided a reason categorized as "other."

Level of Assistance and Physician Interaction

Of the 1048 users for which the level of assistance was known, 791 (75%) received some assistance, and more than half of the 791 (58%) talked to a physician about MEVACOR™ OTC before starting to use. Assistance may have included interactions with a study coordinator acting as a pharmacist, or the Heart Health System personnel administering eligibility assessment questions, or a physician, or all of the above.

Of the 360 participants in the Post-CUSTOM survey who used other OTC products, 82% (296) believed that MEVACOR™ OTC treated a more serious health problem than the other OTC products they used.

Comments:
The data from the study show that the majority of consumers needed a health care provider's advice when making a decision to use lovastatin. It is clear from the data that those who talked to their physicians achieved more accurate self-selection than those who did not. This is of concern if this product were to become available OTC.

Subgroup Analysis of User Decisions Based Upon Label Criteria

The following demographic groups were evaluated:

- Males versus Females
- Caucasians versus Non-Caucasians
- Younger users (age < 65 years) versus Older users (age ≥ 65 years)
- Low Literacy Users versus Literate Users

Although behavior was generally similar across all demographic groups, the sample sizes of some subgroups were small. Therefore, these data may not be generalizable to non-CUSTOM-related groups. Table 21 below summarizes adherence to label benefit criteria by demographic subgroups, based on the sponsor's DAP analyses.

Table 21. Adherence to Label Benefit Criteria by Demographic Subgroups

	Adherence to Label Benefit Criteria (AL†)		
Demographic Subgroups	Initial Use Decision % (N)*	Follow-up Cholesterol Test % (N)*	De-selection due Emergent Events for 26 Weeks % (N)**
Males	42.8% (269/629)	32.8% (206/629)	61.1% (121/198)
Females	50.2% (216/430)	32.6% (140/430)	63.3% (107/168)
Caucasians	46.7% (405/867)	35.2% (305/867)	62.5% (193/309)
Non-Caucasians	42.4% (78/184)	20.6% (38/184)	60.0% (33/55)
Age ≥ 65 years	56.8% (154/271)	43.9% (119/271)	62.7% (64/102)
Age < 65 years	42.0% (331/788)	28.8% (227/788)	62.1% (164/264)
Low Literacy	41.2% (56/136)	29.4% (40/136)	60.5% (26/43)
Non Low Literacy	46.6% (428/918)	33.2% (306/923)	62.5% (200/320)
Total	45.8% (485/1059)	32.7% (346/1059)	62.3% (228/366)

* Number of subjects for each category may differ depending on the number of subjects with missing data
** Denominator for the subgroups is a total number of subjects in a subgroup experiencing emergent event
† AL: According to label

Comments:
There were some differences among the analyzed demographic subgroups; however, none of them were statistically significant. With respect to initial use decision and follow-up cholesterol test, greater percentages of elderly Users compared to those < 65 years of age, and normal literacy compared to low literacy Users adhered to label benefit criteria. More Caucasians compared to non-Caucasian Users adhered to the label benefit criteria with respect to the follow-up cholesterol test. The overall adherence to the label was of concern, ranging from 45.7% for the initial self-selection to 32.9% by the end of the study (de-selection by Week-26) (see Table 16).

Were the Ancillary Materials Available to the Users Helpful?
In addition to the self-selection and compliance with treatment, the sponsor assessed usefulness of additional materials used in the study. A total of 967 Users responded to questions about what materials they looked at, and their assessment of the usefulness of the items. Most Users reported that the shelf display materials were very or somewhat useful (893/967, 92.3%). The most viewed product package materials were the drug package (903/967, 93.4%) and the Quick Start Guide (828/967, 85.6%), followed by the booklet (727/967, 75.2%) and package insert (542/967, 56%).

All of the package materials were rated as very or somewhat useful by almost all Users who read them (93.5%-98.5%). Only 124 (12.8%) of the 967 Users looked at the product website, but most of those that went on the website felt it was very or somewhat useful (103/124, 83.1%). Most of the 258 Users who reported joining the Heart Health Program looked at the newsletters

(186/258, 72.1%), and 88.7% (165/186) of those that looked at the newsletters reported that the newsletters were very or somewhat useful. Of the 241 Users who reported receiving the video; 166 viewed it, and 87.3% (145/166) of those who viewed the video believed it was very or somewhat useful.

Users in this study were concerned about their cholesterol. Eighty-one percent of the 1030 Users who completed the end-of study behavior questions said they had discussed their cholesterol concerns with a physician at some time: 62% within the year before starting the study, and 74% within two years of starting the study. More than half (56.4%) of the 1030 Users reported that they talked to a physician about their taking MEVACOR™ OTC while they were participating in the study.

Of the 2111 non-purchasers 22% (471) reportedly talked with their physician about using the product before deciding not to purchase, and of the 1205 purchasers 42% (504) said they talked with their physician about using the product before deciding to take the first dose.

A total of 31% (359/1146) of participants who had high LDL-C or high triglycerides and responded to the question about physician interaction reported that they interacted with a physician regarding MEVACOR™ OTC.

Comments:
Even though the majority of participants liked additional study materials, their behavior did not translate into good decision making. Data show that consumers had difficulty making a decision themselves to use MOTC. Out of the 485 subjects who self-selected appropriately (the sponsor's definition "according to label") 86% stated that they consulted with a physician, and only 68 (14%) made a correct decision on their own. Forty-two percent (42%) of the participants in the study did not take the first dose until they obtained advice from their physician. The sponsor states that these data suggest that the MEVACOR™ OTC Self-Management System motivated participants to interact with their physician regarding cholesterol management. This may be true for those subjects who have a personal physician, but it is not clear what consumers without health insurance or those who do not have a personal physician would do. Data on how consumer behavior was influenced by having access to a learned intermediary was not collected. It is unclear how the sponsor would implement this OTC Self-Management System outside the boundaries of this clinical study.

Physician Referral Follow-Up Cohort

A total of 127 participants received the advice and follow-up letter recommending that they contact their physician because they had LDL-C > 170 mg/dL or triglycerides > 200 mg/dL, and had either sought assistance at the point of initial purchase, or incorrectly purchased the product but sought post-purchase assistance. Fifty-eight (58) of the 127 provided follow-up information. Nearly two-thirds (36/58) of them reported they had visited or called their physician since their visit to the study site, and most of those (32/36) discussed cholesterol management with their physician. Of the 32 participants who discussed cholesterol management with their physician, 20 reported that they did so because of the advice/letter they received from the Physician Referral portion of the MEVACOR™ OTC Self-Management System in the study. About four-

fifths (25/32) of the participants who discussed cholesterol management with their physician were placed on a new treatment plan, and about three-quarters (19/25) of those placed on a new treatment plan were prescribed a lipid-lowering drug. The drug was a statin in 18 of the 19 participants who received a prescription for a lipid-lowering drug.

Other Behavior Assessments

At the final study site visit, Users of MEVACOR™ OTC were asked if they ever made an effort to lower their cholesterol by eating healthy foods or exercising. Ninety-seven percent of Users (1030/1061) provided a response to this question, and 79.6% (820/1030) had previously tried to lower their cholesterol by eating healthy foods or exercising.

When the Users were asked if they changed their diet and exercise habits while taking MEVACOR™ OTC, the majority responded that they did not change their eating (57.6%) or exercise (70.7%) habits; 40.3% reported eating healthier foods, and 23.7% reported exercising more. A total of 2.1% reported eating less healthy foods, and 5.6% reported exercising less.

The MEDFICTS Dietary Assessment scores at pre-treatment and post-treatment collected to determine if Users maintained a healthy diet confirmed the above observations:

- At baseline, 82% (677/820) of Users were already following a Step 1 (cholesterol intake < 300 mg/day) or Step 2 diet (cholesterol intake < 200 mg/day).
- 56% (80/143) of Users who had not been on either a Step 1 or Step 2 diet prior to the study had MEDFICTS scores that indicated they were following a Step 1 or 2 diet by the end of the study.
- 48% (140/292) of Users who were following a Step 1 diet at baseline were following a Step 2 diet by the end of the study.
- 83% (318/385) of Users who were following a Step 2 diet at baseline maintained their Step 2 diet throughout the study

Comment:
Data show that participants of the study were relatively highly motivated to follow a healthy lifestyle prior to and during the study.

What Was the Change in Cholesterol with Lovastatin 20 mg?

Data summarizing available information about percent change from baseline in cholesterol values is summarized in Table 22. Additional details concerning the data for LDL-C are presented in Table 23. The median reduction in LDL-C achieved in the population who used MOTC was 20.6%. Further reduction, 25.2%, was observed in the cohort of 243 Users that fasted at the baseline and the end of study.

Table 22. Summary of LDL-C, HDL-C, and Total Cholesterol

		Baseline	End of Study	% Change from Baseline
LDL-C	N	931	878	811
	Median (mg/dL)	155	120	-20.6
	25th, 75th Percentiles	132, 180	100, 144	-34.4, -5.0
HDL-C	N	1015	932	906
	Median (mg/dL)	45	45	0
	25th, 75th Percentiles	37, 55	37, 54	-9.5, 10.0
Total-C	N	1053	962	957
	Median (mg/dL)	243	204	-14.6
	25th, 75th Percentiles	218, 271	179, 232	-24.9, -4.6

Table 23. Summary of LDL Cholesterol by Fasting Status

	Fasting Status*	N	Median (mg/dL)	25th, 75th Percentiles
Baseline (n=931)	Fasted	378	165	142, 188
	Not fasted	551	146	126, 173
	Unknown	2	198	NA
End of Study (n=878)	Fasted	608	118	100, 142
	Not fasted	267	122	102, 148
	Unknown	3	133	NA
% Change from Baseline (n=811)	FF	243	-25.2	-38.4, -9.0
	NF	324	-19.7	-32.4, -3.3
	FN	83	-20.7	-37.7, -8.8
	NN	156	-16.5	-32.2, -2.2
	Unknown	5	-25.8	NA

* FF: fasted both at baseline and End of Study; NF: did not fast at baseline and fasted at End of Study; FN: fasted at baseline and did not fast at End of Study; NN: did not fast at either time point.

The distribution of the 1059 Users by baseline and end of study LDL-C is presented in Table 24. Of the 878 Users with a known LDL-C value at the end of the study and who had known LDL-C value at baseline, 548 (62.4%) were at the LDL-C goal level of < 130 mg/dL.

Table 24. Counts of LDL-C Results: Baseline vs. End of Study (Users)

	End of Study						
Baseline	< 100	100-129	130-159	160-170	>170	Unknown	**Total**
< 100	38	17	3	0	1	6	65
100-129	47	58	26	1	2	10	144
130-159	69	123	54	10	10	44	310
160-170	10	31	22	10	7	15	95
> 170	28	88	84	22	50	45	317
Unknown	16	23	16	6	6	61	128
Total	208	340	205	49	76	181	1059

Comments:
The efficacy information gathered during the study has to be interpreted with caution because there was no control group and compliance with the treatment was not enforced or monitored. There was a higher proportion of people at baseline with non-fasting cholesterol values than at the end of the study.

The study results show that the majority of the enrolled subjects had lowered their LDL cholesterol level. According to the sponsor's definition, a total of 548 (62.4%) Users with known LDL-C levels at the end of the study achieved the LDL-C goal (< 130 mg/dL) by the end of the study. This number includes 160 Users whose LDL-C level at baseline was < 130 mg/dL and 39 Users whose LDL-C level at baseline was unknown. We do not know what benefit, if any this subpopulation derived from the treatment. If we deduct these 199 (160+39) Users, the percentage of Users achieving benefit by the end of the study decreases to 39.7% (349/878).

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

The majority of Users of Mevacor in the study lowered their cholesterol.

With respect to behavior end-points of the study, the study results show poor consumer understanding of self-treatment of hypercholesterolemia. The majority (69%) of participants who made a decision to purchase Mevacor needed more information; 37% of purchasers did not know their cholesterol and 18% chose to use it. Of those who stated that they knew their cholesterol level, half could not identify it correctly. The most disturbing results are in self-selection. Over 80% of subjects in the study did not self-select appropriately, as defined by the label. Only 484 Users initially self-selected correctly according to the label and of those only 68 were able to do this without a physician's input. Nearly 1/3 of all Users (51% of women and 11% of men) had a 10-year risk for CHD < 5%. The pre-purchase screening measures may have enhanced the appearance of appropriate self-selection.

Compliance with follow-up cholesterol test rate could have been better; 63% of Users obtained at least one follow-up test during 6 months of the study, but only 33% obtained it within the specified time interval of 4 to 12 weeks. Only 26.6% of Users achieved the target LDL-C goal of < 130 mg/dL within 4 to 12 weeks of the study, and an additional 9% achieved the goal outside the 4 to 12 week time period.

Consumers were restricted to purchasing a maximum of 4 cartons of Mevacor, which may have influenced the efficacy results. Diaries were not collected and this could have impacted compliance information gleaned from the study.

Of the 484 participants, who based on the sponsor's DAP analysis self-selected according to the label, 297 achieved the LDL-C goal (< 130 mg/dL) at the end of the study. Of the 68 participants, who initially self-selected correctly according to the label criteria without a physician interaction, 41 achieved the target LDL-C goal (< 130 mg/dL) at the end of the study. Thus, of the 1059 Users, 41 (4%) correctly, independently achieved the target LDL-C < 130 mg/dL.

7 INTEGRATED REVIEW OF SAFETY

This section of review will focus on safety data gathered during the Actual Use Study #084.

7.1 Methods and Findings

All 1061 Users who reported taking at least one dose of study medication were included in the assessment of safety.

Table 25 displays the number of participants on study drug, by dose and duration of treatment. The range of days on drug displayed in Table 25 does not actually mean that subjects were on drug all of that time; rather, it indicates that subjects had drug in their possession for the specific number of days. The study drug therapy stop date was not recorded by or asked of the participant. The last date the participant returned drug to the study site was used in lieu of a study drug therapy stop date in the calculation of duration of treatment. If a participant's final study drug was returned via the mail, then their therapy stop date was the date that drug was received by the investigator. For those participants that were lost to follow-up, their therapy stop date was equal to the last date of contact (i.e., last study site visit or phone call). In addition, participants did not record the number of 20 mg tablets they took each day; therefore, the labeled daily dose of 20 mg is presented. The mean duration of exposure to lovastatin 20 mg "based on the therapy stop date" was 148.3 days (range 1 to 290 days).

Table 25. Number of Patients on Study Drug by Dose and Duration of Treatment

	1 to 28 days	29 to 56 days	57 to 84 days	85 to 112 days	113 to 140 days	141 to 168 days	≥ 169 days	Total
Lovastatin 20 mg	53	79	50	100	43	80	656	1061

Comments:
The methodology to assess drug exposure is flawed. The study duration was relatively short considering that the drug is to be used indefinitely. It is not clear when the stop treatment date was relative to the user's last dose of the study drug; this information was not collected. There were no diaries used in the study. Data on drug accountability was not provided by the sponsor. Therefore, the extent of exposure to the study drug may be overestimated and not reliable. This makes any safety signals even more relevant and also means that the study may not have been able to provide as much information on safety in actual use as it may appear to do.

At the agency's request, the sponsor submitted additional data on the number of tablets participants purchased during the study. The extent of exposure by the number of tablets dispensed to participants is much lower than the sponsor's initial calculations. The mean duration of exposure "based on the number of tablets dispensed" becomes 122 days assuming no more than one tablet was used per day. When the calculation takes into account the number of tablets participants returned at their last visit, the mean duration of exposure becomes 112.9 days. Distribution of subjects by the number of tablets dispensed is as follows:

- *294 (28%) - 45 tablets,*
- *176 (17%) - 90 tablets,*

- *132 (13%) - 135 tablets,*
- *454 (43%) - 180 tablets,*
- *3 (0.3%) - 225 tablets.*

Table 26 summarizes the number (%) of subjects with clinical adverse experiences, drug-related adverse experiences, serious adverse experiences, serious drug-related adverse experiences, and adverse experiences that caused discontinuation from the study.

Table 26. Adverse Experience Summary

	Lovastatin 20 mg (N=1061)	
Number (%) of subjects	N	(%)
With one or more adverse experiences	452	42.6
With no adverse experience	609	57.4
With drug-related adverse experiences	180	17.0
With serious adverse experiences	28	2.6
With serious drug-related adverse experiences	1	0.1
Who died	1	0.1
Discontinued due to adverse experiences	125	11.8
Discontinued due drug-related experiences	102	9.6
Discontinued due to serious adverse experiences	7	0.7
Discontinued due to serious drug-related experiences	1	0.1

Overall, 452 (42.6%) subjects had at least one adverse experience; of these, 180 had drug-related experiences as determined by an investigator. Twenty-eight reported serious adverse experiences, one of which was drug-related. Seven of the 28 discontinued from the study due to the serious adverse experiences, one of which was drug related.

One of the non drug-related serious adverse experiences resulted in death. One hundred twenty-five (11.8%) patients discontinued drug therapy due to an adverse experience. Of these, 102 discontinued drug therapy due to a drug-related adverse experience.

7.1.1 Deaths

One death occurred in the study. This was a 50-year-old male with a history of atrial fibrillation and high blood pressure who developed a massive stroke. The patient began a regimen of lovastatin 20 mg, once daily on 07-DEC- 2002. Concomitant therapy included Coumadin. On 06-APR-2003 (Day 121 of treatment) the patient experienced a stroke and was hospitalized. Upon hospitalization the patient was administered alteplase, recombinant tissue plasminogen activator, and his lovastatin therapy was discontinued. Subsequently, the patient experienced massive bleeding into the brain and was placed on life support. On 08-APR-2003 the patient was declared brain dead by his attending physician. The patient was taken off all life support and died within minutes. The reported cause of death was due to a massive stroke. The reporting physician determined that the massive stroke and subsequent death were probably not related to study drug therapy.

7.1.2 Other Serious Adverse Events

There were 30 participants who experienced at least one serious clinical adverse event while on lovastatin 20 mg, of which 2 were reported as pre-study adverse experiences. Seven of the 28 participants, had serious adverse experiences that led to discontinuation of drug therapy; however only 1 of these events (Hypersensitivity NOS), was assessed as being drug related.

7.1.3 Dropouts and Other Significant Adverse Events

A total of 360 (33.9%) subjects out of 1061 Users discontinued prior to the end of the study. One hundred twenty-five (11.8%) reported that they discontinued therapy due to a clinical adverse experience (see Table 26). Of these, 102 (9.6 %) adverse experiences that resulted in discontinuation were considered by the study investigator to be drug related. Seven (0.7%) subjects discontinued study therapy due to serious adverse experiences. Fifteen participants reporting discontinuation of therapy due to a clinical adverse experience continued in the study to completion. These participants were counted as "completers" of the study because they returned for their final scheduled visit. As mentioned earlier, the date of the last dose taken was not recorded.

7.1.3.1 Overall profile of dropouts

The following is a disposition of the 360 User dropouts from the study:

Adverse clinical experience	108 (30.0%)
Deviation from protocol occurred	2 (0.6%)
Lost to follow-up	13 (3.6%)
Moved	18 (5.0%)
Withdrew consent	157 (43.6%)
Discontinued for other reasons	53 (14.7%)
Uncooperative	9 (2.5%)

In addition to 360 discontinued subjects, there were 50 subjects with no known use decision who were lost to follow-up after the initial purchase of the study drug.

7.1.3.2 Adverse events associated with dropouts

Adverse experiences resulting in discontinuation of therapy are summarized by body system in Table 27.

Adverse experiences resulting in study therapy discontinuation most often occurred in the categories of Musculoskeletal and Connective Tissue Disorders (6.3%) and Gastrointestinal Disorders (2.8%). The most frequently reported adverse experiences resulting in study therapy discontinuation were Myalgia (3.7%) and Arthralgia (1.2%). Thirty-nine subjects discontinued because of myalgias. Of these, 30 (77%), reported that they recovered by the time the trial concluded. Of the 9 participants with unresolved muscle symptoms, 1 reported 2 events of myalgia (1 event resolved by the end of the study and the other did not). This participant was

counted among 9 participants that did not recover from their symptoms by the end of the study. Eight (21%) of the 39 who discontinued due to myalgias also had a previous history of muscle pain and of these participants, 6 had resolution of their muscle symptoms by the end of the study.

Table 27. Number (%) of Subjects Discontinued Therapy due to Clinical Adverse Experience by Body System

	Users (N=1061) N (%)
Subjects with one or more adverse experience	125 (11.8)
Subjects with no adverse experience	936 (88.2)
Cardiac Disorders	2 (0.2)
Ear and Labyrinth Disorders	1 (0.1)
Gastrointestinal Disorders	30 (2.8)
General Disorders and Administration Site Conditions	14 (1.3)
Immune System Disorders	1 (0.1)
Infections and Infestations	1 (0.1)
Investigations	4 (0.4)
Metabolism and Nutrition Disorders	1 (0.1)
Musculoskeletal and Connective Tissue Disorders	67 (6.3)
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	1 (0.1)
Nervous System Disorders	15 (1.4)
Psychiatric Disorders	4 (0.4)
Reproductive System and Breast Disorders	3 (0.3)
Respiratory, Thoracic and Mediastinal Disorders	5 (0.5)
Skin And Subcutaneous Tissue Disorders	8 (0.8)
Vascular Disorders	4 (0.4)

7.1.3.3 Other significant adverse events

There were no other safety issues associated with dropouts.

7.1.4 Other Search Strategies

Refer to section 2.4 of this review.

7.1.5 Common Adverse Events

Table 28 summarizes clinical adverse experiences by body system that occurred at an observed incidence of ≥ 2%. Although the same subject may have had 2 or more adverse experiences in a body system, the subject is counted only once within a body system category total.

Table 28. Number (%) of Subjects with Adverse Experiences by Body System (Incidence ≥ 2%)

	Lovastatin 20 mg N=1061	
	n	%
Subjects with one or more adverse experiences	452	42.6
Subjects with no adverse experience	609	57.4
Gastrointestinal Disorders	94	8.9
General Disorders and Administration Site Conditions	40	3.8
Infections and Infestations	89	8.4
Injury, Poisoning and Procedural Complications	24	2.3
Musculoskeletal and Connective Tissue Disorders	184	17.3
• Arthralgia	41	3.9
• Myalgia	74	7.0
• Pain in extremity	21	2.0
Nervous System Disorders	44	4.1
Psychiatric Disorders	22	2.1
Respiratory, Thoracic, and Mediastinal Disorders	37	3.5
Skin and Subcutaneous Tissue Disorders	27	2.5
Vascular Disorders	22	2.1

The most common types of adverse experiences were those occurring in the Musculoskeletal System (17.3%). The most frequently reported adverse experiences were myalgia, arthralgia, and pain in extremity.

7.1.5.1 Eliciting adverse events data in the development program

Adverse event information during the actual use study was collected in several ways:

- Subjects who purchased only one box of the study medication and did not return to the study site by Week-12, and those users that did not return for the Week-26 visit, were contacted by the nurse-investigator.
- Participants had an opportunity to return to the study site for repurchase of medication at which time they were asked by the study investigator if they experienced any discomfort since the last visit.
- At the last visit (Week-26) all participants were given a questionnaire which included questions about the adverse experiences.

All serious adverse events were reported to the study physician at the toll-free physician services.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor did not describe what "dictionary" was used to categorize the reported adverse events by preferred terms.

7.1.5.3 Incidence of common adverse events

The most frequently reported adverse experiences were myalgia, arthralgia, and pain in extremity.

7.1.5.4 Common adverse event tables

There were a total of 890 adverse events reported during the study. The most common adverse events by frequency (>1%) irrespective to relationship to the study drug in decreasing incidence are listed in Table 29 below.

Table 29. Most Common Adverse Events (>1%) Reported During the Course of the Study

Adverse Event by Preferred Term	Number of AEs (N = 1061) N (%)
Myalgia	95 (9.0%)
Arthralgia	52 (4.9%)
Pain in extremity	27 (2.6%)
Flatulence	21 (2.0%)
Diarrhea NOS	19 (1.8%)
Headache	18 (1.7%)
Back pain	17 (1.6%)
Sinusitis NOS	15 (1.4%)
Muscle weakness NOS	15 (1.4%)
Hypertension NOS	15 (1.4%)
Dizziness	15 (1.4%)
Rash NOS	14 (1.3%)
Dyspepsia	13 (1.2%)
Cough	13 (1.2%)
Abdominal pain upper	13 (1.2%)
Chest pain	11 (1.0%)
Bronchitis	11 (1.0%)

7.1.5.5 Identifying common and drug-related adverse events

Table 30 (Appendix VI) displays clinical adverse experiences determined by the investigator to be possibly, probably, or definitely related to study medication. Although the subject may have had 2 or more adverse experiences in a body system, the subject is counted only once within a body system category total.

There was a relatively low incidence of drug-related clinical adverse experiences in each body system category except for “Musculoskeletal and Connective Tissue Disorders (8.8%),” and “Gastrointestinal Disorders (5.4%).” The most frequently reported drug-related clinical adverse experiences were myalgia (5.4%), flatulence (1.7%), arthralgia (1.5%), headache (1.2%), and muscle weakness (1.1%).

Comment:
CPK levels were not measured in subjects developing muscle weakness or pain. This is one of the deficiencies of the study.

7.1.5.6 Additional analyses and explorations

The sponsor analyzed the overall distribution of subjects who reported an adverse experience and those with specific drug-related clinical adverse experiences by the subject's self-selection and de-selection behavior classifications. There were some numerical differences in the incidence of subjects with drug-related clinical adverse experiences in the Musculoskeletal and Connective Tissue Disorder body system category. There were higher proportions of Users with drug-related musculoskeletal adverse events in the MUSM NAS (not acceptable safety) subgroup compared to the MASM AL (according to label) subgroup based on their self-selection and de-selection behavior. However, no conclusions can be drawn from the observed differences since there were no placebo or control groups, and the number of events in each subgroup was relatively small.

7.1.6 Less Common Adverse Events

An assessment of the incidence of less common adverse events in the actual use study is not possible because:

- the number of subjects treated in the actual use trial is relatively small to detect infrequent adverse events
- there was no control group, and
- methodology for assessment of extent of exposure and compliance with the treatment were not reliable.

7.1.7 Laboratory Findings

There were no serious laboratory adverse experiences.

The only laboratory safety test required by the protocol was ALT measurements.

Of the 1061 subjects that took at least 1 dose of study medication, 986 subjects were included in the population that had a laboratory test post-baseline. Five (0.5%) of the subjects had one or more laboratory adverse experiences during the study. The laboratory adverse experience profile is summarized in Table 31.

Table 31. Laboratory Adverse Experience Summary

	Users (N=1061)	
Number (%) of subjects	N	%
With at least one laboratory test post baseline	986	
With one or more adverse experiences	5	0.5
With no adverse experience	981	99.5
With drug-related adverse experiences	4	0.4
With serious adverse experiences	0	0.0
With serious drug-related adverse experiences	0	0.0
Who died	0	0.0
Discontinued due to adverse experiences	1	0.1
Discontinued due to drug-related adverse experiences	1	0.1
Discontinued due to serious adverse experiences	0	0.0
Discontinued due to serious drug-related adverse experiences	0	0.0

Drug-related increased ALT (Normal Range 10-40 U/L) occurred in 4 out of 986 (0.4%) subjects (Table 31). One of them discontinued due to an ALT of 59 U/L (ULN = 40 U/L), and an AST of 53 U/L (ULN = 40 U/L). No follow-up was required as per protocol. Three subjects had an ALT that was > 3 x ULN at the end of the study. All 3 had a repeat ALT: 2 on the repeat test had values below 1 x ULN and the third had a value of 43 U/L.

Comment:
Although follow up was not required, it appears that it was done for the 3 subjects who did not discontinue.

7.1.7.1 Overview of laboratory testing in the development program

See section 7.1.7.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

There was no control group in the study. Therefore, drug-control analyses were not performed.

7.1.7.3 Standard analyses and explorations of laboratory data

Table 32 summarizes the ALT values for all users in the study.

Table 32. Summary of Serum Alanine Aminotransferase (ALT) Values

	End of Study					
Baseline	ALT≤1xULN	1xULN<ALT ≤2xULN	1xULN<ALT ≤2xULN	ALT>3xULN	Unknown	Total
ALT≤1xULN	860	46	3	2	96	1007
1xULN<ALT≤2xULN	20	19	3	1	6	49
Unknown	5	0	0	0	0	5
Total	885	65	6	3	102	1061

At baseline testing, 1007 of 1061 (94.9%) subjects had an ALT test result less than or equal to 1 x ULN (40 U/L). Forty-nine (4.6%) had ALT elevations above 1 x ULN at baseline, but were less than or equal to 2 x ULN. There were no Users in the study with a baseline ALT > 3xULN, as this was an exclusion criterion. Of those that entered the study, there were 5 subjects who did not have a baseline ALT value due to investigator or Cholestech machine error. All 5 of them had an End of Study ALT ≤ 1 x ULN.

There were 3 subjects that self-selected to purchase MEVACOR™ OTC, but they were prohibited from leaving the study site with drug as their ALT was > 3 x ULN (135, 154, and 189 U/L). As already discussed, three subjects had an ALT > 3 x ULN for the End of Study ALT (121, 151, and 134 U/L). When re-tested at their next visit, all the ALTs had decreased (22, 29, 43 U/L).

Comment:
Since people with ALT > 3 x ULN were excluded, this study could not provide safety data on this cohort if they had chosen to self-select. This is a concern since there are people with asymptomatic LFT elevations who may choose to take Mevacor if it were sold OTC.

7.1.7.3.1 Analyses focused on measures of central tendency

The mean ALT change from baseline was 3.9 U/L (±10.5 S.D.). As shown in Table 33, 952 subjects were included in both the baseline and end of study calculations. Change from baseline is calculated using the end of study value which was collected between 1 and 290 days.

Table 33. Serum Alanine Aminotransferase (ALT) Change from Baseline

	ALT (U/L)		
	N	Mean (U/L)	Standard Deviation (U/L)
Baseline	1054	23.2	8.9
End of study	957	26.9	12.3
Mean change from baseline	952	3.9	10.5

No predefined limit of change was established for laboratory adverse experiences.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

See section 7.1.7.3 of the review.

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

See section 7.1.7.3 of the review.

7.1.7.4 Additional analyses and explorations

There were no additional analyses or explorations done in the actual use study.

7.1.7.5 Special assessments

There were no special assessments performed in the actual use study.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Blood pressure was collected at baseline for all purchasers in order to calculate 10 year Hard CHD risk. No other vital signs, other physical observations, or special examinations related to safety were performed.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

This was an uncontrolled actual use study. Therefore, drug-control comparisons were not done.

7.1.8.3 Standard analyses and explorations of vital signs data

There were no analyses done on vital signs data.

7.1.8.3.1 Analyses focused on measures of central tendencies

Not applicable.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Not applicable.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There were no drop-outs due to vital sign abnormalities.

7.1.8.4 Additional analyses and explorations

Not applicable.

7.1.9 Electrocardiograms (ECGs)

ECGs were not done during the actual use study.

7.1.10 Immunogenicity

Immunogenicity of the tested drug was not assessed in the actual use study.

7.1.11 Human Carcinogenicity

There were no data on human carcinogenicity submitted to this application.

7.1.12 Special Safety Studies

There were no new special safety studies submitted to this application.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There are no published reports on the recreational use of lovastatin. Furthermore, there are no reports to the Worldwide Adverse Experience System (WAES) Database where lovastatin was the primary suspect agent that could be construed as evidence of drug abuse. Based on the drug's pharmacological properties and the extensive knowledge of the drug's clinical adverse experience profile, there is no information to suggest that the drug has the potential to be abused.

Comment:
There are no data that the use of lovastatin has a potential for abuse or withdrawal phenomena.

7.1.14 Human Reproduction and Pregnancy Data

No new data on human reproduction and pregnancy were submitted to this application. Lovastatin is a Pregnancy Category X drug. In a submission to the prescription lovastatin NDA 19-643/S-061 dated March 31, 2004 the sponsor requested to change lovastatin's Pregnancy Category from X to C. The request was denied due to insufficient data to support the change. Even though the proposed OTC label targets women at least 55 years of age, the results of actual use study #084 show that 37.4% of women below this age chose to use the drug.

7.1.15 Assessment of Effect on Growth

There were no assessments of effects on growth in this application.

7.1.16 Overdose Experience

Overdose information on lovastatin is summarized from three sources:

1. exposure and/or overdose reports received at regional poison control centers and summarized in the Toxic Exposure Surveillance System (TESS) by the American Association of Poison Control Centers (AAPCC);
2. cases of deliberate or accidental overdose reported to Merck through the Worldwide Adverse Experience System (WAES) Database; and
3. published literature.

The term "exposure" is used throughout this section to identify calls or reports to poison control centers or to the WAES. Not all of these exposure reports were actually true cases of overdosage.

The sponsor states that based on preclinical studies, there is a wide margin of safety with lovastatin. In mice, the median lethal dose for oral lovastatin is > 15 g/m^2. In mice and rats, on a per-kilogram basis, the acute LD50 values were > 20 grams/kg and > 5 grams/kg, respectively. The usual recommended starting prescription dose of lovastatin is 20 mg per day and the recommended dosing range is 10 to 80 mg/day. Using the 60-kg conservative estimate for body weight in an average adult, the daily lovastatin starting dose would be 0.33 mg/kg. Assuming an average adult to be 60 kg, the rat LD50 based on dose per kilogram corresponds to > 15,000-fold above the starting dose. Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patients had any specific symptoms, and none had sequelae. The maximum dose taken was 5 to 6 g. If a patient weighing 60 kg took 6000 mg lovastatin orally, the dose normalized to body weight would be 100 mg/kg orally.

Lovastatin has occasionally been used in extremely high doses in studies evaluating its potential anti-tumor activity in cancer patients. In a Phase II study, 16 patients with advanced gastric adenocarcinoma received lovastatin 35 mg/kg/day for 7 days. Gastrointestinal dysfunction was the most commonly observed adverse experience and mild myalgia and muscle weakness with increased CK levels was considered the most severe clinical toxicity. In another study of 88 patients with advanced solid tumors who were given lovastatin in dose-escalating 7-day courses ranging from 2 to 45 mg/kg/day, doses up to 25 mg/kg were well tolerated.

The sponsor states, that from all sources, including the published literature, there have been no known reports of overdosage with a fatal outcome involving lovastatin as the sole agent. There are 4 known cases with fatal outcome involving potential overdose with lovastatin and concomitant agents. These 4 cases were reported to AAPCC and will be discussed in the Exposures from Poison Control Centers.

1. Review of the American Association of Poison Control Centers Data

The AAPCC collects data from poison control centers in 48 states and the District of Columbia and tabulates this information in the TESS Database. In 1985, AAPCC started providing general information about the clinical outcomes of exposures and first started to tabulate symptom information in 1993. Because of problems with verification, AAPCC does not routinely document the quantity of drug consumed in exposure cases.

Lovastatin was approved for United States marketing in 1987 and the first exposure cases were documented by AAPCC in 1988.

Table 34 (Appendix VII) displays the number of lovastatin exposures reported to the AAPCC by year from 1988 through 2002. During that 15-year period, there were 4612 exposures to lovastatin reported to poison control centers. Of the total exposures, 3254 episodes involved lovastatin as a single agent. The estimated number of lovastatin prescriptions in the United States based on IMS (Intercontinental Marketing Services) data is also shown for each year.

During the same 15-year time period, there were estimated to be over 100 million prescriptions for lovastatin prescribed to patients with hypercholesterolemia.

There were 4 deaths reported to AAPCC from 1988 through 2002 involving lovastatin taken with other agents. There have been no fatal overdose exposure cases reported to AAPCC involving lovastatin as the sole agent.

The first fatal exposure occurred in a 28-year-old male patient with a history of paranoid schizophrenia and polysubstance abuse. The patient presented to the clinic with hematemesis, mild abdominal pain, nausea and vomiting following 4 days of anorexia. His medications included lovastatin 20 mg, niacin 1000 mg 3 times a day, aspirin 325 mg 3 times a day, and NAVANE™ (thiothixene) 40 mg at nighttime and 10 mg as needed for agitation. He also took COGENTIN™12 mg at bedtime and 150 mg of desipramine. The patient was known to hoard all his medicines, especially niacin. A serum screen showed desipramine and acetaminophen at a concentration of 2 mcg/mL. Laboratory data showed elevation in AST (6700 units) and ALT (7900 units) with a bilirubin of 6.4 mg/dL. The patient's hospital course was that of fulminant hepatic failure with coma, seizures, renal failure, and coagulopathy. He expired 36 hours after admission. Postmortem examination showed massive acute hepatic necrosis with acute renal tubular necrosis. AAPCC identified nicotinic acid as the primary agent and lovastatin as the secondary agent and categorized the exposures as an adverse drug reaction.

The second fatal exposure was that of a suicide in a 42-year-old male who ingested ~80 pills identified as controlled-release diltiazem and lovastatin (dose not specified) 7 hours prior to hospitalization. The patient's initial vital signs included a blood pressure of 50 to 60 mm Hg and a pulse of 61 beats/minute. Serum chemistries were normal except for hypokalemia (3.2 mEg/L). Following calcium gluconate, glucagon, external pacing, and initiation of a 20-mcg drip of dopamine, blood pressure improved to 110 mm Hg and pulse to 71 beats per minute. The patient was transferred to a critical care unit where he went into asystole and died shortly after arriving. Toxicology laboratory tests for drugs of abuse, acetaminophen, and aspirin were negative. AAPCC identified diltiazem as the primary agent in the exposure and lovastatin as the secondary agent.

The third fatal exposure was that of a suicide in a 75-year-old male with a recent diagnosis of Alzheimer's disease. He ingested the following agents in a suspected suicide attempt: lorazepam, hydroxyzine hydrochloride, cimetidine, lovastatin (dose not specified), hydrochlorothiazide, and ethanol. The patient was found pulseless and apneic by paramedics. Emergency treatment included vasopressors, fluids and electrolytes, and anti-arrhythmic therapy. QRS was 0.04 seconds, potassium was 1.6 mmol/L, and bicarbonate was 19 mmol/L. Acetaminophen and salicylate were not detected and blood alcohol was 95 mg/dL. Despite maximal support, he developed renal failure with elevated CPK (2033 IU/L). Two days following admission he became hypotensive and a decision was made to withdraw life support. AAPCC identified lorazepam as the primary agent in the exposure and lovastatin as a secondary agent.

The fourth fatal exposure occurred in a 78-year-old male patient with a history of cerebrovascular accident (CVA) with left hemiparesis, diabetes mellitus, and depression. In an apparent suicide attempt, the patient ingested unknown quantities of the following agents: metformin, glipizide, acarbose, terazosin hydrochloride, lisinopril, gabapentin, hydroxyzine hydrochloride, dipyridamole, lovastatin (dose not specified), and finasteride. He was intubated by EMS and transferred to a critical care unit. His family confirmed that the patient's medicine bottles had been emptied. The patient was acidotic (blood pH = 6.9; bicarbonate = 3 mEq/L) and sodium bicarbonate therapy was administered. Despite treatment, the patient's acidosis worsened. He became more hypotensive, bradycardic, and hypothermic and was treated with multiple vasopressors. The patient subsequently became hypoglycemic (blood glucose <20 mg/dL) and developed lactic acidosis (26 mmol/L). His family declined hemodialysis and treatment for low blood sugar and the patient expired. AAPCC identified metformin as the primary agent and lovastatin as a secondary agent.

Considering all exposure categories (lovastatin single and multiple agents), accidental (unintentional) events represented the largest category for reason for exposure according to data collected by AAPCC for the 1988 through 2002 time period. The inappropriate use of lovastatin with other agents for suicide attempts or other misuse or abuse was very uncommon for the years 1988 through 2002, representing ~7% of the total exposures (4612) reported to regional poison control centers.

With single-agent exposures of lovastatin, accidental exposures also represented the largest category for reason for exposure. Of the total exposures for the years 1988 through 2002, ~95% were listed as accidental (unintentional). The misuse of lovastatin (single agent) as a drug involved in suicide attempts or other misuse or abuse was very uncommon, representing < 3% of the total single-agent exposures (3254) reported to poison control centers.

AAPCC defines a medical outcome as a clinical effect in a patient that resulted in one of the following: no effect, minor effect, moderate effect, major effect, death, and an "other" category. During the 1988 through 2002 time period, the largest category of outcomes (54.8% of total exposures) was "other," which includes in part the sub-classifications of "not followed, nontoxic" and "not followed, minimal clinical effects." The combined categories of "no effect" or "minor effect" represent ~43.2% of the total reports for the years 1988 through 2002. There were 17 reports with a "major" effect (0.4% of the total reports).

For lovastatin single-agent exposures, the largest category of outcomes (59.1% of total exposures) for the 15-year period 1988 through 2002 was the category "other". The largest subcategories in this group were "not followed, nontoxic" and "not followed, minimal clinical effects". The combined categories "no effect" or "minor effect" accounted for ~40.5% (1319 patients) of the total outcomes. There were 11 patients who had moderate effects (0.9%).

There was 1 patient who had major effects that were considered life threatening or produced disability as a result of lovastatin exposure. This patient was a 64-year-old male who presented to the hospital with an adverse reaction of rhabdomyolysis while on lovastatin. The duration of clinical effects was not reported. Following treatment with intravenous fluids, the patient's

symptoms resolved. Lovastatin was discontinued and the patient was released from the hospital. There have been no reports in the Toxic Exposure Surveillance System from 1988 through 2002 that identified an overdose fatality with lovastatin as the sole agent.

AAPCC began to tabulate the duration of clinical effects in overdose exposures beginning in 1993. The largest category within medical outcomes was identified as "other," which is a broad category designation that included predominately "not followed, nontoxic" and "not followed, minimal clinical effects." The second most common category of classification was "no effect."

With the lovastatin "all exposures" cases for the 1993 through 2002 time frame, the clinical effects considered moderate resolved in 1 month or less in the 51 cases where a duration was specified. In addition, 1 case with moderate outcome had a duration recorded as "anticipated permanent." The remaining 7 moderate cases had a duration of "unknown," "missing," or "invalid." A large majority of the moderate cases resolved in $\leq$ 3 days. Twelve of the 14 cases classified as "major" were evaluated for duration and resolved in $\leq$ 1 week.

With the single-agent lovastatin exposures for the 1993 through 2002 time frame, the clinical effects for those exposures identified as moderate resolved in $\leq$ 3 days in 6 cases and $\leq$ 1 week in 1 case, out of 7 cases where a specific duration was evaluated. In addition, 1 case with moderate outcome had a duration recorded as "anticipated permanent." The remaining 2 moderate cases had a duration of "unknown," "missing," or "invalid." There was 1 case where the clinical outcome was classified as "major" for the 1993 through 2002 time frame; the duration of clinical effect was not reported in this case.

AAPCC Tabulations of Specific Symptoms Associated With Lovastatin Exposures
The AAPCC began to tabulate specific symptoms associated with overdose exposures in 1993. In their tabulations and reports, the AAPCC refers to these symptoms as "clinical effects." The TESS database lists symptoms in 8 major body system categories (cardiovascular, dermal, gastrointestinal, heme/hepatic, neurological, ocular, renal, respiratory) and a miscellaneous category. The miscellaneous group identifies 18 additional symptoms, including "other." In total, the AAPCC database contains 118 separate symptom terms.

A patient with 2 symptoms (for example nausea and drowsiness) for a single exposure would have been counted under 2 different symptom terms. It is assumed that any one particular symptom (for example, tachycardia or vomiting) was tabulated only once for a particular patient for an overdose incident. Therefore, for purposes of calculating an estimate of the proportion of patients with a given symptom/sign, the assumption has been made that the count for a given symptom term equates reasonably well with the number of patients who reported to have had or were observed to have had that particular symptom. Finally, the data from AAPCC does not identify patients who had more than one exposure in the same year or in multiple years. It is assumed that such a patient would be treated in the database as any other exposure case and counted again. All symptoms associated with lovastatin all exposures and lovastatin single-agent exposures, whether or not related to the exposure, were examined. There were 686 symptoms reported in association with 3285 all-exposures cases (single-agent plus lovastatin with other agents) and 216 symptoms associated with 2251 lovastatin single-agent exposures during the 10-

year period 1993 through 2002. From an examination of all 8 major body symptom categories, there was no specific clustering of symptoms within a category associated with lovastatin single agent or lovastatin all exposures.

Based on the all-exposure category for the period 1993 through 2002, a reporting cutoff (number reported for a specific symptom ÷ number of exposures) of ≥ 0.4 % was selected for inclusion by the sponsor. All symptoms that were reported at a frequency of ≥ 0.4% among the "all exposures" and single-agent exposures are presented in Table 35. The denominator used in constructing this proportion was the total patients with an outcome over the 10-year period. In the miscellaneous effects category, the designation of "other" symptoms was tabulated because it had the greatest number of symptoms counts. Selected symptoms related to the potential of lovastatin to cause muscle toxicity (muscle weakness, rhabdomyolysis, CPK elevated) or hepatic dysfunction ("AST/ALT increase > 100 units < 1000 units" term and "AST/ALT >1000 units" term combined) were also tabulated under the heading of "selected symptoms." These selected symptoms are displayed regardless of the reporting rate (i.e., symptom included if there was at least one occurrence in the TESS database from 1993 through 2002).

Table 35. Number of Symptoms Associated with Lovastatin: All Exposures and Single Agent Exposures (Reporting Rate of ≥ 0.4%)

		Total for 1993 through 2002 All Exposures N=3285		Total for 1993 through 2002 Single-Agent Exposures	
Symptom category	Symptoms	N	%	N	%
Cardiovascular Effects	Bradycardia	15	0.5	0	0
	Hypotension	19	0.6	0	0
	Tachycardia	29	0.9	5	0.2
Dermal	Erythema/flushed	18	0.5	6	0.3
Gastrointestinal Effects	Abdominal pain	16	0.5	8	0.4
	Diarrhea	27	0.8	15	0.7
	Nausea	36	1.1	16	0.7
	Vomiting	54	1.6	19	0.8
Neurological effects	Agitation/irritable	17	0.5	6	0.3
	Confusion	17	0.5	5	0.2
	Dizziness/vertigo	28	0.9	8	0.4
	Drowsiness/lethargy	77	2.3	17	0.8
	Headache	10	0.3	4	0.2
Miscellaneous effects	Other	70	2.1	36	1.6
Selected signs and symptoms	AST/ALT increase	5	0.2	4	0.2
	CPK elevated	2	0.1	0	0
	Muscle weakness	9	0.3	3	0.1
	Rhabdomyolysis	3	0.1	2	0.1
Total symptoms		686	10.9	216	9.6

There were 3285 exposures involving either lovastatin as a single agent or lovastatin with other agents during 1993 through 2002. The symptom with the greatest number of reports was drowsiness/lethargy (2.3% reporting rate), followed by miscellaneous/other (2.1%). Other than drowsiness/lethargy, the most common CNS symptom was dizziness/vertigo (0.9%). The most common cardiovascular symptom was tachycardia at 0.9%. In the GI category, the proportions of patients with nausea, vomiting, and diarrhea were 1.1, 1.6, and 0.8%, respectively. During the

time frame 1993 through 2002, there were 5 cases (0.2%) out of 3285 exposures of abnormal liver function tests (AST/ALT increased), 9 cases (0.3%) of muscle weakness, 3 cases (0.1%) of rhabdomyolysis, and 2 cases (0.1%) of CPK elevations. In general, the proportion of symptoms observed with all exposures (multiple- and single-agent) was somewhat higher than that observed with single-agent lovastatin exposures.

During the time frame 1993 through 2002, there were 4 cases of abnormal liver function tests (AST/ALT increased) reported out of 2251 exposures, as well as 3 cases of muscle weakness, and 2 cases of rhabdomyolysis.

Exposure of Lovastatin in Children < 6 Years of Age
From 1988 through 2002, there were 3001 accidental (unintentional) ingestions involving lovastatin (all exposures) in children < 6 years of age, of which 2342 were reports on lovastatin as a single agent. There were 5 additional exposures in this age group involving lovastatin (all exposures) for reasons other than accidental ingestion; 2 of these were reports on lovastatin as a single agent.

There were no deaths in children < 6 years old associated with overdose exposures due to lovastatin as a single agent or when ingested with other drugs. The largest category of medical outcome was "other," representing 49.6% of the total exposures for the years 1988 through 2002. After the "other" category, the next 2 largest categories of outcomes were the "no effect" category with 1422 cases (47.3%) of lovastatin ingestion (all exposures) and the "minor effect" category with 82 cases (2.7%) that were judged to have produced minor clinical effects. There were no cases judged to have a major clinical outcome, although there were 10 cases assessed to have moderate clinical outcome over the 15-year period beginning in 1988.

For the lovastatin single-agent exposures in children <6 years, the largest category of clinical outcomes was the "other" category, which represented 53.5% of all clinical outcomes for the years 1988 through 2002. The second largest category of clinical outcomes was "no effect" and this was 44.6% of all effects. There was 1 case in which the clinical outcome was moderate. No cases had major clinical effects and there were no deaths reported in children < 6 years of age as a result of lovastatin single-agent exposures.

2. WAES Data Review of Overdoses

The Worldwide Adverse Experience System is a Merck Research Laboratories database that compiles adverse experiences on Merck products including overdoses from around the world.

The sponsor searched the WAES database for reports of potential overdose with lovastatin by querying for the following preferred terms: accidental exposure, accidental overdose, accidental overdose (non-therapeutic agent or chemical), accidental overdose (therapeutic agent), accidental poisoning, alcohol poisoning, anticonvulsant toxicity, drug toxicity, drug toxicity NOS, ergot poisoning, exposure to toxic agent, exposure to toxic agent (non-occupational), gas poisoning, non-accidental overdose, overdose, overdose NOS, poisoning deliberate, prescribed overdose, or therapeutic agent toxicity. Since lovastatin was approved for prescription use in 1987 through

01-Nov-2003, there have been 41 spontaneous reports with one or more of these terms reported to Merck from health care professionals and entered into WAES. It should be noted that not all of these cases document actual instances of lovastatin overdose. Two of these reports involved overdoses of other drugs with lovastatin as a concomitant therapy taken at the therapeutic dose. Another report documents "possible acetaminophen toxicity," but does not include any indication that the patient was exposed to an overdose of lovastatin. A fourth report describes a patient who took a glyburide tablet rather than her customary lovastatin dose.

Among these 41 WAES reports are 6 cases with fatal outcome. Five of the 6 fatal outcome reports involved lovastatin exposure with concomitant drugs:
(1) an overdose of lovastatin and diltiazem in a suicide attempt;
(2) an overdose of warfarin with lovastatin taken at a therapeutic dose;
(3) an exposure to lovastatin (dose unknown) with possible acetaminophen toxicity;
(4) an overdose of lovastatin and other suspected therapies in an apparent suicide attempt, and
(5) an overdose of lovastatin and other suspected therapies in a suspected suicide attempt.
In the sixth case with fatal outcome, a 36-year-old female experienced 4 miscarriages while her husband was on treatment with lovastatin.

Three of the 6 cases were reported to AAPCC and were documented in the published literature. These 3 cases also have been discussed previously in the previous section of the review.

There is one additional case with fatal outcome that is not included among the 41 WAES reports discussed above, but was reported to AAPCC and published in the clinical literature. Information received in the published article has been entered into the WAES database, but the report was not identified by the overdose query since it did not contain any of the preferred terms defined by the search strategy. AAPCC identified nicotinic acid as the primary agent and lovastatin as the secondary agent and categorized the exposures as an adverse drug reaction.

Therefore, a total of 7 unique cases with fatal outcome have been identified that were either classified as "overdose" in the WAES query or reported to AAPCC (or both). In 3 of these cases, it appears that the patient was not actually exposed to an overdose of lovastatin. None of these 7 cases suggest a cause for concern with lovastatin OTC.

The remaining 35 cases identified as overdose in WAES were nonfatal reports. The amount of lovastatin involved in 11 exposure cases was unknown, and among the remaining cases, the reported amount of lovastatin taken varied from 10 mg to as much as 1040 mg in 2 cases, one of which reported no symptoms. The second case was a 3 year old female who accidentally ingested 1040 mg of lovastatin; back pain was the only symptom reported but the final outcome is unknown.

With regard to symptoms associated with lovastatin overdoses, there were no symptoms reported in 12 of the 35 cases. Symptoms related to skeletal muscle such as myositis, muscle pain, rhabdomyolysis, and laboratory findings of an elevated creatine phosphokinase were observed in 7 listed individuals, all of which involved lovastatin with other agents. The outcome of the exposure has also been tabulated and these data show that at the time of the report, 16 individuals

had recovered/improved from the exposure and 17 individuals had the outcome listed as "unknown." Two patients had not recovered; other agents were involved in their overdose exposure.

Published Reports of Lovastatin Overdoses
Since lovastatin has been marketed through 01-Nov-2003, there have been 4 reports in the published literature of overdose in patients exposed to lovastatin. All 4 cases involved individuals who attempted suicide by ingesting lovastatin with concomitant drugs and were published in the Annual Reports of the AAPCC and are summarized in the previous section of the review.

Comments:
Data on overdose with lovastatin's supports its wide margin of safety. To date, there are no deaths reported due to a single overdose of lovastatin.

7.1.17 Postmarketing Experience

Postmarketing safety data will be reviewed by reviewers in the Division of Metabolic and Endocrine Drug Products.

7.2 Adequacy of Patient Exposure and Safety Assessments

The safety profile of lovastatin was extensively studied and characterized during its approval as prescription product, and since, in the post-marketing period. No new signals have appeared in the course of the Rx-to-OTC switch development program. The proposed OTC label contains all appropriate drug interaction warnings. However, use in OTC setting has the potential to result in unexpected adverse events in the future. Of great concern, is the potential use of lovastatin by women of childbearing age, particularly since many were Users in the CUSTOM study.

Use of lovastatin by consumers with LDL-C levels outside the range specified in the label, is also a safety issue. The risk/benefit ratio of this therapy for those with LDL-C below 130 mg/dL may be unfavorable. On the other hand, even though some benefit may be achieved for consumers with LDL-C above 170 mg/dL, the risk of treatment with a sub-therapeutic OTC dose of lovastatin is also unclear. Finally, consumers with underlying liver disease and those taking interacting medications also may be at risk. It is unclear how a consumer with asymptomatic liver disease would know not to use Mevacor.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The safety of lovastatin in the target OTC population was evaluated in the Actual Use Study, CUSTOM. No additional new clinical safety studies have been submitted to this NDA.

7.2.1.1 Study type and design/patient enumeration

Refer to section 7.1 of this review.

7.2.1.2 Demographics

Refer to section 6.1.4 of this review.

7.2.1.3 Extent of exposure (dose/duration)

Refer to section 7.1 of this review.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No other new studies to support lovastatin 20 mg use in target OTC population have been submitted to this NDA.

7.2.2.2 Postmarketing experience

As of March 26, 2004, lovastatin has received marketing approval in 59 countries. Mevacor is not available without a prescription in any country. It has been withdrawn from the market in 13 countries, none withdrawn for any safety reasons.

7.2.2.3 Literature

There are no literature reports submitted to this NDA to support lovastatin's safety.

7.2.3 Adequacy of Overall Clinical Experience

Refer to section 7.1 of this review.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No data on special animal or In Vitro testing have been submitted to this NDA.

7.2.5 Adequacy of Routine Clinical Testing

Refer to section 7.1 of this review.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Metabolic, clearance, and interaction tests were conducted during the development program to support lovastatin's approval as prescription drug. No additional data have been submitted to this NDA.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Refer to section 7.1 of the review.

7.2.8 Assessment of Quality and Completeness of Data

Refer to section 7.1 of this review.

7.2.9 Additional Submissions, Including Safety Update

No additional safety data have been submitted to this NDA since it's submission on August 24, 2004.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Safety data gathered from the Actual Use study is consistent with the safety profile of lovastatin as a prescription drug.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed nonprescription dose of lovastatin is 20 mg once daily with the evening meal. The usual recommended prescription starting dose is 20 mg daily with the evening meal. Single daily doses of lovastatin given with the evening meal are more effective than the same dose given in the morning.

In order to assess the cholesterol-lowering effect of MEVACOR™ OTC, consumers are instructed by the proposed nonprescription label to have a cholesterol test after 6 weeks of treatment. If the LDL-C target goal of < 130 mg/dL has been achieved, consumers are further instructed to continue using drug along with diet and exercise. If they do not reach the LDL-C target goal, users are instructed to stop taking MEVACOR™ OTC and talk to their physician.

Comment:
The proposed 20 mg dose of lovastatin has been shown to be efficacious in lowering serum cholesterol. Whether the untitrated 20 mg is the effective dose for the target OTC population, will be addressed by the Division of Endocrine and Metabolic Drug Products.

8.2 Drug-Drug Interactions

Several drugs (cyclosporine, clarithromycin, itraconazole, ketoconazole, nefazodone, erythromycin, and HIV protease inhibitors) have the potential to interact with lovastatin when administered concomitantly. These drugs and grapefruit juice, are strong CYP3A4 inhibitors, and may increase plasma HMG-CoA inhibitory activity levels, and therefore may increase the individual's risk of myopathy. In addition, gemfibrozil and niacin may also increase the risk of myopathy through a different mechanism.

8.3 Special Populations

Lovastatin is a pregnancy Category X drug. The sponsor has requested to change this classification to Category C. The data to support this request was submitted to the lovastatin prescription NDA 19-643. The only new data presented in support of the change was a limited postnatal neurodevelopment assessment following direct dosing of neonatal rats. FDA reviewed the data and found that information presented was inadequate to support a labeling change from pregnancy Category X to Category C.

Worrisome, is the fact that 50% of women enrolled in the actual use study were less than 55 years of age; 37.4% of women users were less than 55 years and 11% were under 45 years. These data demonstrate that women of childbearing age erroneously chose to take Pregnancy Category X Mevacor OTC.

8.4 Pediatrics

The sponsor requested a waiver to the pediatric requirement because the product does not represent a meaningful benefit to pediatric patients.

The proposed OTC label directs that this product is for men 45 years of age and older and women 55 years of age or older. It is clear from the results of the study that the package label poorly communicates the message not to use the drug if the consumer is under these ages. Lovastatin use in adolescent population (10 to 17 years of age) will remain under the prescription label. Lovastatin use in the prepubertal pediatric population has not been studied.

8.5 Advisory Committee Meeting

An Advisory Committee Meeting to discuss the appropriateness of lovastatin Rx-to-OTC switch was held.

8.6 Literature Review

There were no literature reports submitted to support this application.

8.7 Postmarketing Risk Management Plan

The sponsor is proposing to market lovastatin OTC under the conditions similar to the actual use study:

- Sales restricted to the pharmacies only,
- Pharmacist acting in a role of a health care provider, advising consumers how to self-select and use the product, as well as providing access to serum cholesterol testing.

Currently, FDA has no control over the practice of pharmacies, and has no regulatory authority to enforce over-the-counter drug sales to pharmacy outlets only. The sponsor states that the Self Management System used in the actual use study will also be implemented upon the approval of Mevacor for OTC marketing. It is unclear how the sponsor will guarantee the presence of a medical staff and functional Cholestech machine in pharmacies where this product would be sold if approved.

8.8 Other Relevant Materials

9 OVERALL ASSESSMENT

9.1 Conclusions

The current paradigm for the treatment of hypercholesterolemia is individualized, based on serum cholesterol levels and the presence of certain number of risk factors for CHD. The results of the Actual Use study show that the majority of consumers cannot correctly self-select to use lovastatin without an input of a health care provider. It is not clear, whether this difficulty is related to the label used in the study, the complexity of the treatment guidelines, or both.

The study as conducted gave unreliable information about consumer compliance with the daily dosing regimen.

Unresolved issues related to OTC marketing of lovastatin remain:

- Poor appropriate consumer self-selection rates based on the label alone,
- Poor compliance with the follow-up cholesterol test and the issue of treatment to an LDL-C goal,
- Pregnancy Category X and potential use of the drug by women of childbearing age (a risk demonstrated by errors in self-selection),
- The need for monitoring of liver function tests,

- A realistic assessment of how consumers would dose themselves and for how long a duration,
- Risk/benefit for people with < 5% 10-year risk for CHD.

Thus, the potential benefit/risk ratio for this drug if it is switched from Rx to OTC becomes difficult to characterize based upon the "Use" data.

9.2 Recommendation on Regulatory Action

In the opinion of this reviewer, the data of the Actual Use study CUSTOM leave too many questions unanswered. This application should not be approved.

9.3 Recommendation on Postmarketing Actions

No recommendations on postmarketing action are appropriate based upon the recommendation.

9.3.1 Risk Management Activity

No recommendations on the need of post-marketing risk management activities are appropriate based upon the recommendation.

9.3.2 Required Phase 4 Commitments

No recommendations on the need of Phase 4 commitments are appropriate at this time.

9.3.3 Other Phase 4 Requests

See section 9.3.2 of this review.

9.4 Labeling Review

The proposed labeling is being reviewed in detail by an interdisciplinary scientist in the Division of Over-the-Counter Drug Products. In addition, a Label Comprehension study to assess comprehension of the proposed label is being reviewed by Laura Shay, RN, MS, C-ANP.

The proposed label is not in conformance with the format and content requirements for over the counter drug product labeling as specified in 21 CFR 201.66.

The same label was used in the Actual Use Study CUSTOM. It is clear from the study results that the majority of consumers were not able to follow directions when selecting the product for their own use. Consequently, the proposed label will need major revisions and retesting to assure better consumer understanding.

9.5 Comments to Applicant

The following are comments for the applicant. If the sponsor wishes to pursue this Rx-to-OTC switch:

1. Create as simple a label as possible. Test label comprehension prior to embarking upon an actual use study.
2. Pregnancy Category X is a large safety concern with this drug. It is not clear if this drug could be successfully targeted to just a male OTC population. However, if women would use it off label the pregnancy concern would remain.
3. Correct self-selection, without dependence upon input from a health care provider is very important for an OTC product.

APPENDICES

Appendix I.

Figure 2

Flow Chart of Study Procedures—Initial Storefront Visit

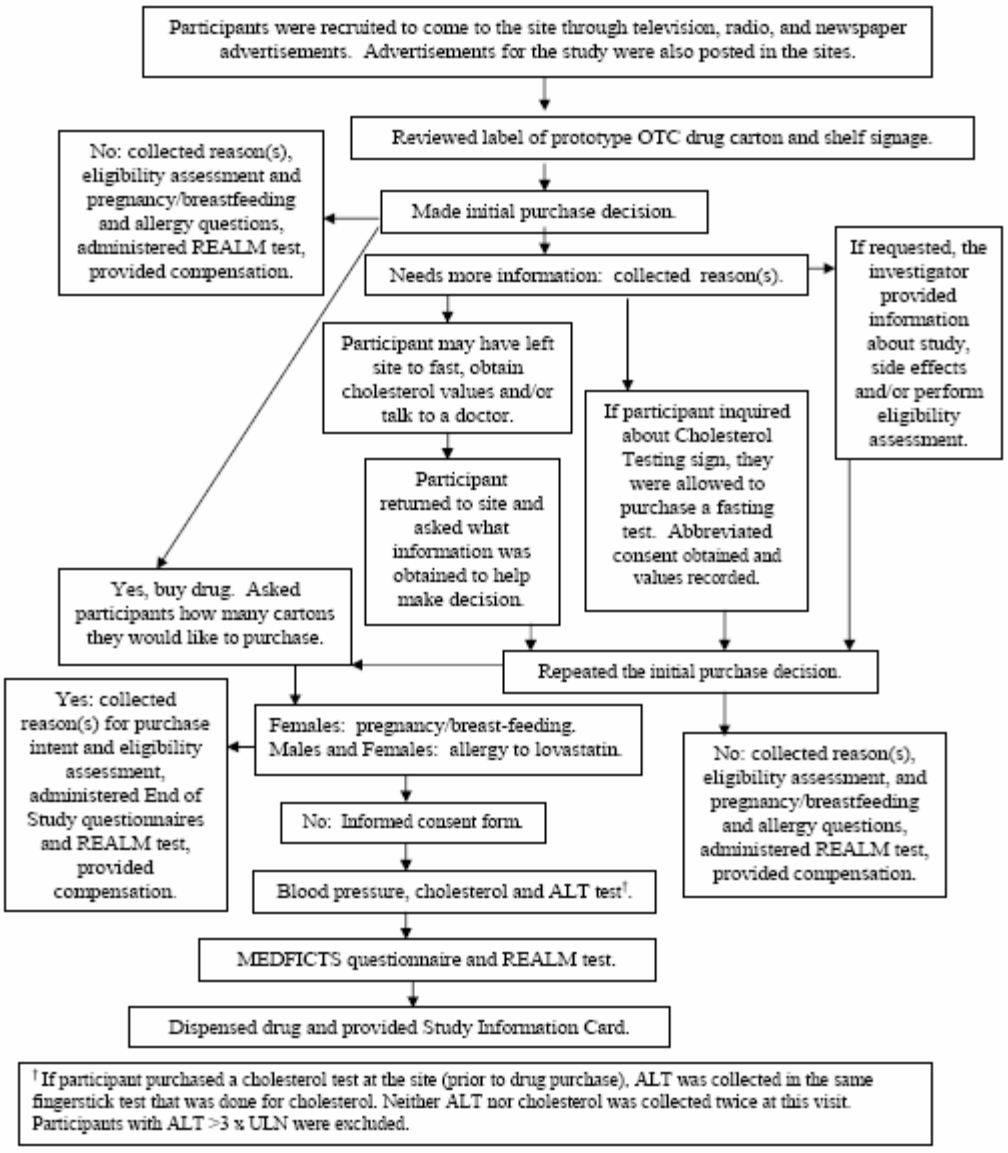
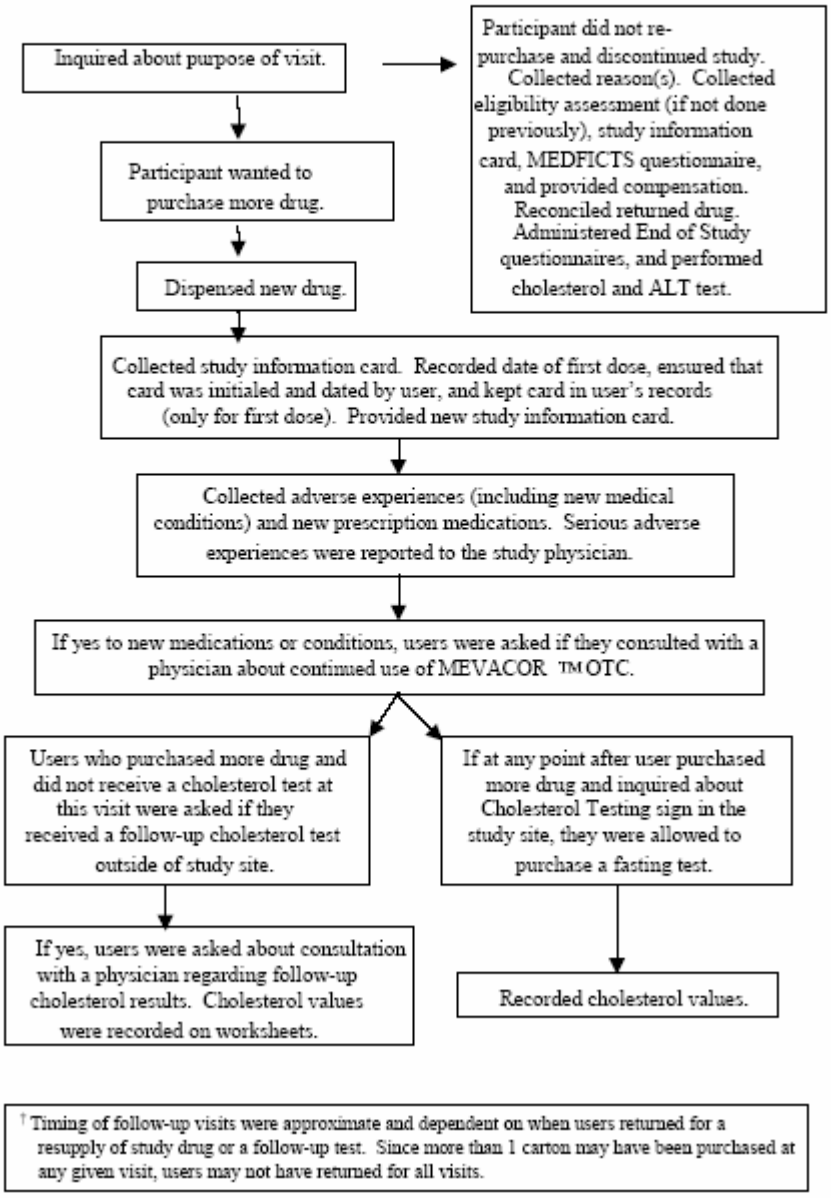


Figure 3

Flow Chart of Study Procedures—
Follow-Up Storefront Visits for Purchasing Drug†



† Timing of follow-up visits were approximate and dependent on when users returned for a resupply of study drug or a follow-up test. Since more than 1 carton may have been purchased at any given visit, users may not have returned for all visits.

Figure 4

Flow Chart of Study Procedures—Follow-Up Storefront Visits for Cholesterol Te

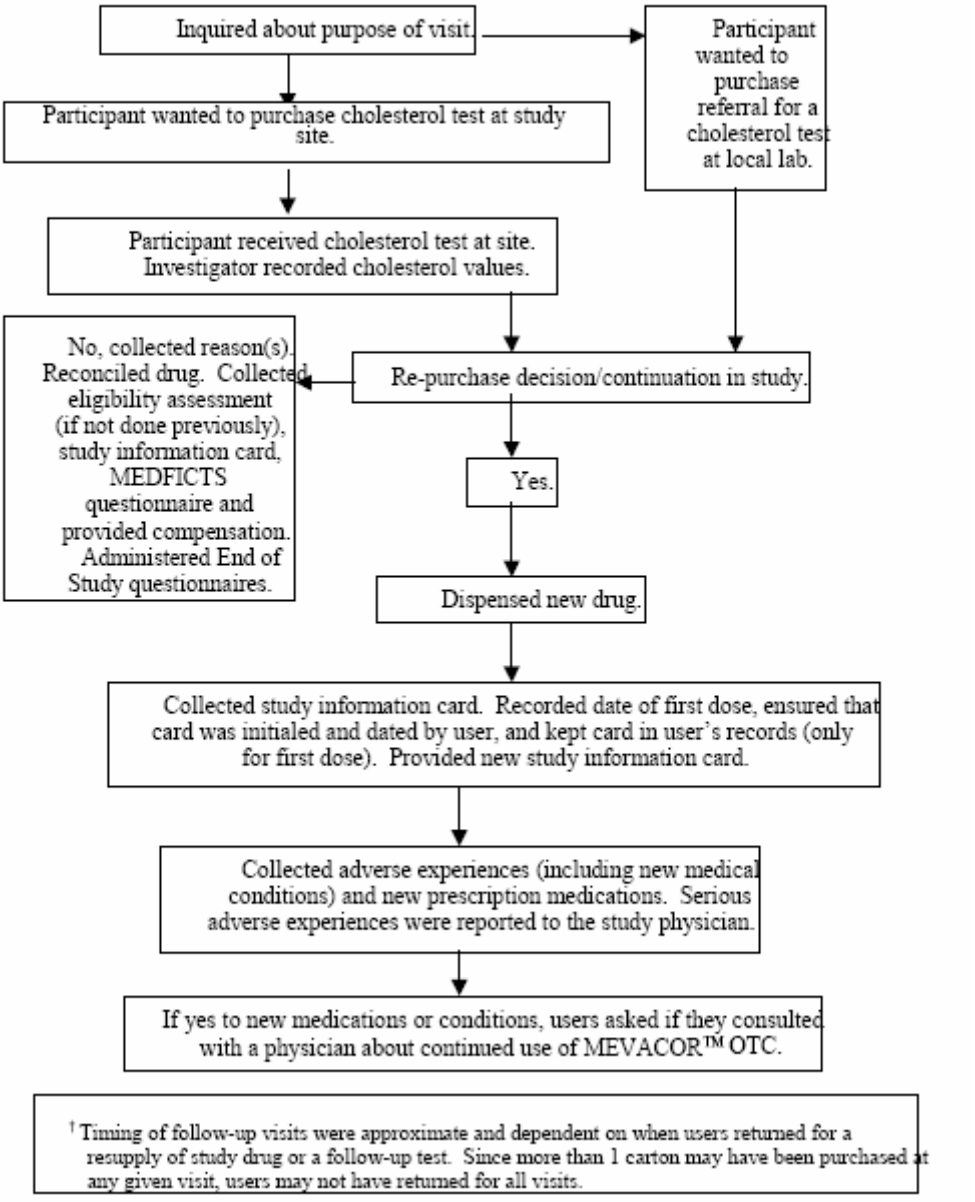
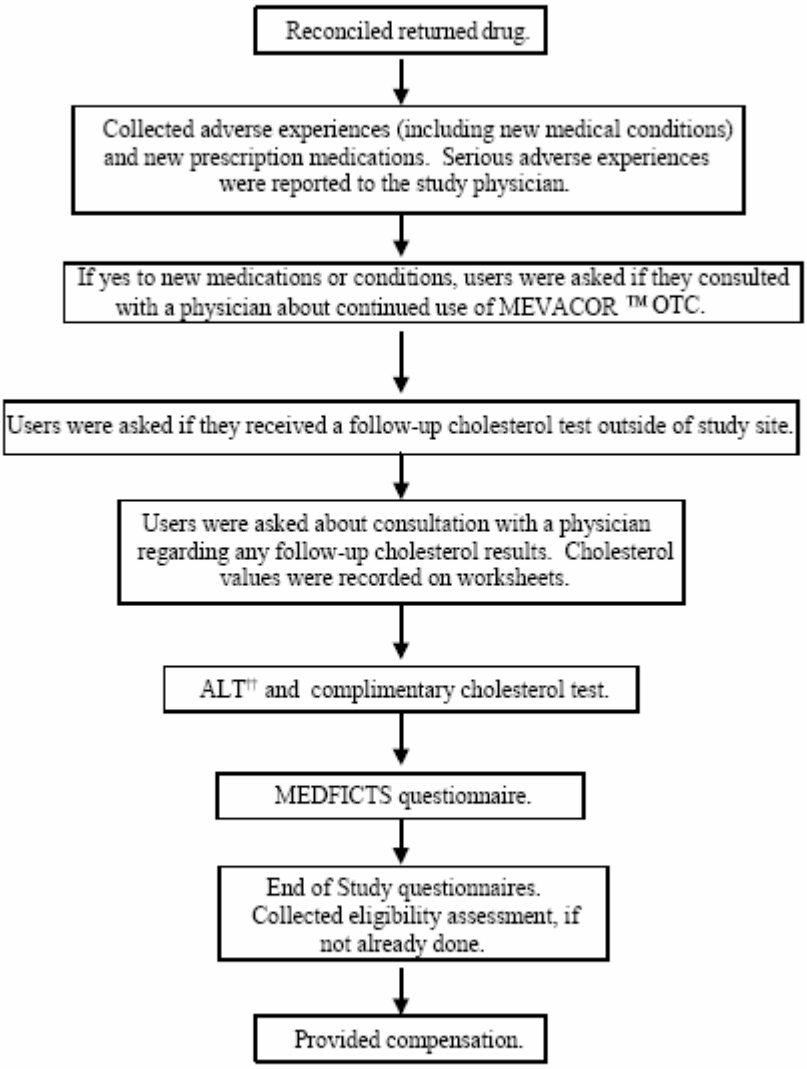


Figure 5

Flowchart of Study Procedures—
Final Storefront Visit†



† If a user completed the study, the final visit occured at approximately 26 weeks after the first visit to the study site.
†† Participants with ALT > 3xULN returned in approximately 2 weeks for follow-up test.

Appendix II.

Table 6. Baseline Participant Characteristics

		Calls (N=11252)	Appointments Kept (N=3346)	Purchase Decision (N=3316)				No Purchase Decision (N=30)
				Purchaser				
				User (N=1061)	Non-User (N=94)	Unknown (N=50)	Non-Purchaser (N=2111)	
Gender	Male	5872 (52.2)	1962 (58.6)	631 (59.5)	52 (55.3)	34 (68.0)	1226 (58.1)	19 (63.3)
	Female	5380 (47.8)	1384 (41.4)	430 (40.5)	42 (44.7)	16 (32.0)	885 (41.9)	11 (36.7)
Age (years)	< 40	1703 (15.1)	457 (13.7)	68 (6.4)	8 (8.5)	9 (18.0)	367 (17.4)	5 (16.7)
	40-44	1291 (11.5)	377 (11.3)	80 (7.5)	5 (5.3)	4 (8.0)	281 (13.3)	7 (23.3)
	45 to 49	1514 (13.5)	461 (13.8)	132 (12.4)	13 (13.8)	5 (10.0)	310 (14.7)	1 (3.3)
	50 to 54	1656 (14.7)	509 (15.2)	179 (16.9)	13 (13.8)	16 (32.0)	297 (14.1)	4 (13.3)
	55 to 59	1399 (12.4)	445 (13.3)	174 (16.4)	8 (8.5)	6 (12.0)	256 (12.1)	1 (3.3)
	60 to 64	1231 (10.9)	413 (12.3)	156 (14.7)	17 (18.1)	6 (12.0)	232 (11.0)	2 (6.7)
	65 to 69	952 (8.5)	303 (9.1)	148 (13.9)	10 (10.6)	2 (4.0)	138 (6.5)	5 (16.7)
	70 to 75	804 (7.1)	234 (7.0)	78 (7.4)	10 (10.6)	2 (4.0)	144 (6.8)	0 (0.0)
	≥ 76	609 (5.4)	145 (4.3)	46 (4.3)	10 (10.6)	0 (0.0)	84 (4.0)	5 (16.7)
	Unknown	93 (0.8)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Racial Origin	Asian	235 (2.1)	68 (2.0)	21 (2.0)	2 (2.1)	2 (4.0)	43 (2.0)	0 (0.0)
	Black	2298 (20.4)	632 (18.9)	90 (8.5)	13 (13.8)	10 (20.0)	513 (24.3)	6 (20.0)
	Hispanic American	632 (5.6)	171 (5.1)	58 (5.5)	5 (5.3)	4 (8.0)	102 (4.8)	2 (6.7)
	Native American	108 (1.0)	23 (0.7)	9 (0.8)	1 (1.1)	1 (2.0)	12 (0.6)	0 (0.0)
	White	7674 (68.2)	2393 (71.5)	869 (81.9)	70 (74.5)	33 (66.0)	1401 (66.4)	20 (66.7)
	Other	120 (1.1)	29 (0.9)	6 (0.6)	3 (3.2)	0 (0.0)	20 (0.9)	0 (0.0)
	Unknown	185 (1.6)	30 (0.9)	8 (0.8)	0 (0.0)	0 (0.0)	20 (0.9)	2 (6.7)
Literacy	Low	NA	NA	136 (12.8)	10 (10.6)	9 (18.0)	255 (12.1)	NA
	Normal	NA	NA	920 (86.7)	64 (68.1)	41 (82.0)	982 (46.5)	NA
	Unknown	NA	NA	5 (0.5)	20 (21.3)	0 (0.0)	874 (41.4)	NA

Appendix III.

Table 7. Prevalence of Specific Label Ineligibility Criteria

Ineligibility Criteria[†]	Made a purchase decision (N=3316)		Non-Purchasers (N=2111)		Purchasers Use Decision (N=1205)						
					User (N=1061)			Non-User (N=94)		Unknown (N=50)	
	N	M[‡]	n	M	n[§]	n[‖]	M[#]	n	M	n	M
Too young	1194	3314	890	2109	147	115	1061	23	94	19	50
Did not know LDL-C cholesterol numbers	1078	2913	732	1783	174	144	1034	24	84	4	12
LDL-C was too low	567	2913	432	1783	60	62	1034	11	84	2	12
LDL-C was too high	551	2913	299	1783	150	75	1034	26	84	1	12
Did not know HDL-C cholesterol numbers	992	2939	679	1799	152	134	1044	23	84	4	12
HDL-C was too high	436	2939	282	1799	83	56	1044	15	84	0	12
Didn't know triglycerides	967	2935	659	1795	153	129	1044	23	84	3	12
Triglycerides were too high	768	2935	468	1795	170	98	1044	25	84	7	12
Taking any Rx medication	1735	2945	1049	1805	313	317	1044	48	84	8	12
Taking potentially interacting drugs[¶]	152	2947	116	1806	12	20	1046	4	84	0	11
Don't know if taking other potentially interacting drugs	44	2947	29	1806	6	7	1046	2	84	0	11
Taking other Rx cholesterol medication	609	2933	424	1801	62	103	1037	19	84	1	11
Don't know if taking other Rx cholesterol medication	3	2933	3	1801	0	0	1037	0	84	0	11
Medical condition: stroke	135	2947	100	1806	16	15	1046	2	84	2	11
Medical condition: heart disease	285	2947	186	1805	37[††]	52	1046	9	84	1	12
Medical condition: liver disease	80	2949	70	1807	3	6	1046	1	84	0	12
Medical condition: diabetes	275	2949	196	1807	30	43	1046	5	84	1	12
Don't have one of the risk factors	1178	2949	712	1807	269	153	1046	36	84	8	12
Have had muscle problem from previous use of cholesterol medication	300	2932	200	1791	53	33	1046	13	84	1	11
Allergic to lovastatin	13	3026	13	1825	0	0	1061	0	90	0	50
Pregnant or breastfeeding	12	3029	12	1828	0	0	2061	0	90	0	50

[†] Participants can be counted in more than one ineligible criteria. [‡] M represents the number of Evaluators, Non-Purchasers, Users, etc. who provided a response on the eligibility assessment. [§] Without Physician Override. [‖] With Physician Override. [¶] Potentially interacting drugs are Nefazodone, Cyclosporine, Erythromycin or Clarithromycin, Ketoconazole or Itraconazole, Gemfibrozil, Protease Inhibitors, Niacin(>1000 mg/day). [#] Includes two (2) protocol violators.
[††] Includes one (1) protocol violator.

Appendix IV.

Table 18. Follow-up Cholesterol Test for Ongoing Use Decision

Adherence to Label Criteria	AL	AB	NAB	NAS	Unknown	Total
Adhered to label criteria	275	37	0	29	5	346
Got a cholesterol test within 4-12 weeks	275	37	0	29	5	346
• LDL-C < 130 mg/dL and continued	225	32	0	23	2	282
• LDL-C ≥ 130 mg/dL and discontinued	17	1	0	3	3	24
• LDL-C ≥ 130 mg/dL and Physician interaction	9	0	0	2	0	11
• Don't know LDL-C, cont., with Phys. Interaction	24	4	0	1	0	29
Closely adhered to label criteria	33	98	0	20	2	153
Got a cholesterol test outside of 4-12 weeks	33	98	0	20	2	153
• LDL-C < 130 mg/dL and continued	7	76	0	10	0	93
• LDL-C ≥ 130 mg/dL and discontinued	2	5	0	1	2	10
• LDL-C ≥ 130 mg/dL and Physician interaction	1	13	0	5	0	19
• Don't know LDL-C, cont., with Phys. Interaction	23	4	0	4	0	31
Did not adhere to label criteria	0	0	391	46	0	437
Got a cholesterol test	0	0	145	15	0	160
• LDL-C ≥ 130 mg/dL and continued	0	0	122	13	0	135
• LDL-C < 130 mg/dL and discontinued - Cured	0	0	0	0	0	0
• Don't know LDL-C, cont., without Phys. interac.	0	0	21	1	0	22
• LDL-C missing, cont., without Phys. interac.	0	0	2	1	0	3
No cholesterol test, cont. without Phys. interaction	0	0	246	31	0	277
Discontinued – Missing Assessment	40	11	0	6	66	123
No cholesterol test‡	37	10	0	5	64	116
• Learned not right	19	3	0	0	29	51
• Physician advised not right	10	1	0	0	11	22
• Other reason for discontinuation	9	6	0	5	26	46
Got a cholesterol test – not a factor in discontinuation	3	1	0	1	2	7
Total	348	146	391	101	73	1059

AL: according to label; AB: adequate benefit; NAB: not adequate benefit; NAS: not adequate safety; ‡Participants may be counted in more than one subgroup.

Appendix V.

Table 20. Number of Participants by Adherence to Label Criteria Emergent Events for Ongoing Use Decision

Adherence to Label Criteria	AL	AB	NAB	NAS	Unknown	Total
Experienced Emergent Events	130	90	102	44	0	366
Adhered to label criteria	128	24	62	14	0	228
Diagnosed with new medical condition and did inform HCP* about MOTC	51	17	32	5	0	105
Began Rx medication and did inform HCP about MOTC	111	19	55	11	0	196
Developed unexplained muscle pain, did D/C MOTC and inform HCP about MOTC	11	2	5	2	0	20
Closely adhered to label criteria	1	66	39	11	0	117
Diagnosed with new medical condition and did not informed HCP about MOTC	1	30	18	4	0	53
Began non-interacting Rx med. and did not inform HCP	1	37	28	6	0	72
Developed unexplained muscle pain, informed HCP but did not D/C MOTC	0	8	1	0	0	9
Developed unexplained muscle pain, D/C MOTC but did not inform HCP	0	12	3	3	0	18
Did not adhere to label criteria	1	0	1	19	0	21
Allergy to MOTC, liver disease, or became pregnant, did not inform HCP	0	0	0	0	0	0
Began interacting Rx med but did not inform HCP	0	0	0	2	0	2
Developed unexplained muscle pain, did not D/C MOTC or inform HCP	1	0	0	15	0	16
Developed CHD, Diabetes or Stroke, did not inform HCP	0	0	1	2	0	3
No Emergent Medical Conditions or Situations	218	56	289	57	73	693
Total	348	146	391	101	73	1059

* HCP: Health Care Provider; AL: according to label; AB: adequate benefit; NAB: not adequate benefit; NAS: not adequate safety.

Appendix VI.

Table 30. Number (%) of Subjects with Drug-Related Clinical Adverse Experiences by Body System

	Users N=1061 (%)
Subjects with one or more adverse experience	180
Subjects with no adverse experience	881
Ear and Labyrinth Disorders	**1 (0.1)**
Tinnitus	1 (0.1)
Gastrointestinal Disorders	**57 (5.4)**
Abdominal distension	3 (0.3)
Abdominal pain NOS	4 (0.4)
Abdominal pain upper	10 (0.9)
Anal hemorrhage	1 (0.1)
Constipation	5 (0.5)
Diarrhea NOS	11 (1.0)
Dry mouth	1 (0.1)
Dyspepsia	7 (0.7)
Eructation	1 (0.1)
Flatulence	18 (1.7)
Gastrointestinal disorder NOS	1 (0.1)
Gastrointestinal irritation	1 (0.1)
Glossodynia	1 (0.1)
Loose stools	3 (0.3)
Nausea	2 (0.2)
Swollen tongue	1 (0.1)
Tongue disorder NOS	1 (0.1)
Vomiting NOS	2 (0.2)
General Disorders and Administration Site Conditions	**16 (1.5)**
Asthenia	4 (0.4)
Chest tightness	1 (0.1)
Fatigue	3 (0.3)
Feeling abnormal	1 (0.1)
Feeling hot	1 (0.1)
Feeling jittery	1 (0.1)
Nodule	1 (0.1)
Edema peripheral	2 (0.2)
Pain NOS	2 (0.2)
Sluggishness	1 (0.1)
Immune System Disorders	**1 (0.1)**
Hypersensitivity NOS	1 (0.1)
Infections And Infestations	**1 (0.1)**
Sinusitis NOS	1 (0.1)
Injury, Poisoning And Procedural Complications	**1 (0.1)**
Epicondylitis	1 (0.1)
Investigations	**1 (0.1)**
Blood pressure increased	1 (0.1)
Heart rate increased	1 (0.1)

Table 30. Number (%) of Subjects with Drug-Related Clinical Adverse Experiences by Body System (cont.)

Musculoskeletal And Connective Tissue Disorders	**93 (8.8)**
Arthralgia	16 (1.5)
Arthritis NOS	1 (0.1)
Back pain	3 (0.3)
Joint swelling	1 (0.1)
Muscle cramp	6 (0.6)
Muscle spasms	1 (0.1)
Muscle stiffness	1 (0.1)
Muscle twitching	2 (0.2)
Muscle weakness NOS	12 (1.1)
Musculoskeletal stiffness	1 (0.1)
Myalgia	57 (5.4)
Neck pain	2 (0.2)
Pain in extremity	9 (0.8)
Pain in jaw	1 (0.1)
Nervous System Disorders	**22 (2.1)**
Burning sensation NOS	1 (0.1)
Depressed level of consciousness	1 (0.1)
Dizziness	7 (0.7)
Headache	13 (1.2)
Paralysis NOS	1 (0.1)
Psychiatric Disorders	**8 (0.8)**
Anxiety	2 (0.2)
Depression	1 (0.1)
Insomnia	4 (0.4)
Nervousness	1 (0.1)
Restlessness	1 (0.1)
Reproductive System And Breast Disorders	**3 (0.3)**
Erectile dysfunction NOS	2 (0.2)
Sexual dysfunction NOS	1 (0.1)
Respiratory, Thoracic And Mediastinal Disorders	**5 (0.5)**
Cough Dyspnea	2 (0.2)
Nasal Congestion	1 (0.1)
Sinus Congestion	1 (0.1)
Skin And Subcutaneous Tissue Disorders	**10 (0.9)**
Acne NOS	1 (0.1)
Contusion	1 (0.1)
Erythema	1 (0.1)
Face edema	1 (0.1)
Rash NOS	6 (0.6)
Vascular Disorders	**1 (0.1)**
Peripheral coldness	1 (0.1)

Appendix VII.

Table 34. Number of Lovastatin Exposures from the Toxic Exposure Surveillance System Database (1988-2002)

	Years															
	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	Total (1998 through 2002)
Estimated number of prescriptions (1000s)	3835	6248	7928	10,338	11,591	11,698	11,480	10,591	9635	7563	4838	3272	2358	1823	2524	105,670
All exposures	40	230	2731	4570	5700	4850	4860	4330	4210	4151	2140	1650	1950	2010	2702	46124
Deaths																
Single-agent exposures	40	170	213	334	435	373	377	336	310	235	144	106	114	111	145	3245
Deaths	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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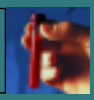
Grundy SM, Cleeman JI, Merz NB, et al. Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation 2004; 110:227-239.

High Blood Cholesterol

Detection



Evaluation

Treatment

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on

Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Executive Summary

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High Blood Cholesterol

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National Cholesterol Education Program

National Heart, Lung, and Blood Institute

National Institutes of Health

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Contents

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Executive Summary

Introduction

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) constitutes the National Cholesterol Education Program's (NCEP's) updated clinical guidelines for cholesterol testing and management. The full ATP III document is an evidence-based and extensively referenced report that provides the scientific rationale for the recommendations contained in the executive summary. ATP III builds on previous ATP reports and expands the indications for intensive cholesterol-lowering therapy in clinical practice. It should be noted that these guidelines are intended to inform, not replace, the physician's clinical judgment, which must ultimately determine the appropriate treatment for each individual.

Background

The third ATP report updates the existing recommendations for clinical management of high blood cholesterol. The NCEP periodically produces ATP clinical updates as warranted by advances in the science of cholesterol management. Each of the guideline reports—ATP I, II, and III—has a major thrust. ATP I outlined a strategy for primary prevention of coronary heart disease (CHD) in persons with high levels of low density lipoprotein (LDL) cholesterol (≥160 mg/dL) or those with borderline-high LDL cholesterol (130-159 mg/dL) and multiple (2+) risk factors. ATP II affirmed the importance of this approach and added a new feature: the intensive management of LDL cholesterol in persons with established CHD. For CHD patients, ATP II set a new, lower LDL cholesterol goal of ≤100 mg/dL. ATP III adds a call for more intensive LDL-lowering therapy in certain groups of people, in accord with recent clinical trial evidence, but its core is based on ATP I and ATP II. Some of the important features shared with previous reports are shown in Table A in the Appendix.

While ATP III maintains attention to intensive treatment of patients with CHD, its major new feature is a focus on primary prevention in persons with multiple risk factors. Many of these persons have a relatively high risk for CHD and will benefit from more intensive LDL-lowering treatment than recommended in ATP II. Table 1 shows the new features of ATP III.

Table 1. New Features of ATP III

Focus on Multiple Risk Factors

- Raises persons with diabetes without CHD, most of whom display multiple risk factors, to the risk level of CHD risk equivalent.
- Uses Framingham projections of 10-year absolute CHD risk (i.e., the percent probability of having a CHD event in 10 years) to identify certain patients with multiple (2+) risk factors for more intensive treatment.
- Identifies persons with multiple metabolic risk factors (metabolic syndrome) as candidates for intensified therapeutic lifestyle changes.

Modifications of Lipid and Lipoprotein Classification

- Identifies LDL cholesterol <100 mg/dL as optimal.
- Raises categorical low HDL cholesterol from <35 mg/dL to <40 mg/dL because the latter is a better measure of a depressed HDL.
- Lowers the triglyceride classification cutpoints to give more attention to moderate elevations.

Support for Implementation

- Recommends a complete lipoprotein profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) as the preferred initial test, rather than screening for total cholesterol and HDL alone.
- Encourages use of plant stanols/sterols and viscous (soluble) fiber as therapeutic dietary options to enhance lowering of LDL cholesterol.
- Presents strategies for promoting adherence to therapeutic lifestyle changes and drug therapies.
- Recommends treatment beyond LDL lowering for persons with triglycerides ≥200 mg/dL.

LDL Cholesterol: The Primary Target of Therapy

Research from experimental animals, laboratory investigations, epidemiology, and genetic forms of hypercholesterolemia indicate that elevated LDL cholesterol is a major cause of CHD. In addition, recent clinical trials robustly show that LDL-lowering therapy reduces risk for CHD. For these reasons, ATP III continues to identify elevated LDL cholesterol as the primary target of cholesterol-lowering therapy. As a result, the primary goals of therapy and the cutpoints for initiating treatment are stated in terms of LDL.

Risk Assessment: First Step in Risk Management

A basic principle of prevention is that the intensity of risk-reduction therapy should be adjusted to a person's absolute risk. Hence, the first step in selection of LDL-lowering therapy is to assess a person's risk status. Risk assessment requires measurement of LDL cholesterol as part of lipoprotein analysis and identification of accompanying risk determinants.

In all adults aged 20 years or older, a fasting lipoprotein profile (total cholesterol, LDL cholesterol, high density lipoprotein (HDL) cholesterol, and triglyceride) should be obtained once every 5 years. If the testing opportunity is nonfasting, only the values for total cholesterol and HDL cholesterol will be usable. In such a case, if total cholesterol is ≥200 mg/dL or HDL is <40 mg/dL, a followup lipoprotein profile is needed for appropriate management based on LDL. The relationship between LDL cholesterol levels and CHD risk is continuous over a broad range of LDL levels from low to high. Therefore, ATP III adopts the classification of LDL cholesterol levels shown in Table 2, which also shows the classification of total and HDL cholesterol levels.

Table 2. ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

LDL Cholesterol	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
≥190	Very high
Total Cholesterol	
<200	Desirable
200-239	Borderline high
≥240	High
HDL Cholesterol	
<40	Low
≥60	High

Risk determinants in addition to LDL-cholesterol include the presence or absence of CHD, other clinical forms of atherosclerotic disease, and the major risk factors other than LDL (see Table 3). (LDL is not counted among the risk factors in Table 3 because the purpose of counting those risk factors is to modify the treatment of LDL.) Based on these other risk determinants, ATP III identifies three categories of risk that modify the goals and modalities of LDL-lowering therapy. Table 4 defines these categories and shows corresponding LDL-cholesterol goals.

Table 3. Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals*

- Cigarette smoking
- Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL)†
- Family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)
- Age (men ≥45 years; women ≥55 years)*

* *In ATP III, diabetes is regarded as a CHD risk equivalent.*

† *HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.*

Table 4. Three Categories of Risk that Modify LDL Cholesterol Goals

Risk Category	LDL Goal (mg/dL)
CHD and CHD risk equivalents	<100
Multiple (2+) risk factors*	<130
Zero to one risk factor	<160

** Risk factors that modify the LDL goal are listed in Table 3*

The category of highest risk consists of CHD and CHD risk equivalents. The latter carry a risk for major coronary events equal to that of established CHD, i.e., >20% per 10 years (i.e., more than 20 of 100 such individuals will develop CHD or have a recurrent CHD event within 10 years). CHD risk equivalents comprise:

- Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease);
- Diabetes;
- Multiple risk factors that confer a 10-year risk for CHD >20%.

Diabetes counts as a CHD risk equivalent because it confers a high risk of new CHD within 10 years, in part because of its frequent association with multiple risk factors. Furthermore, because persons with diabetes who experience a myocardial infarction have an unusually high death rate either immediately or in the long term, a more intensive prevention strategy is warranted. Persons with CHD or CHD risk equivalents have the lowest LDL cholesterol goal (<100 mg/dL).

The second category consists of persons with multiple (2+) risk factors in whom 10-year risk for CHD is ≤20%. Risk is estimated from Framingham risk scores (see Appendix). The major risk factors, exclusive of elevated LDL cholesterol, are used to define the presence of multiple risk factors that modify the goals and cutpoints for LDL-lowering treatment, and these are listed in Table 3. The LDL cholesterol goal for persons with multiple (2+) risk factors is <130 mg/dL.

The third category consists of persons having 0-1 risk factor; with few exceptions, persons in this category have a 10-year risk <10%. Their LDL cholesterol goal is <160 mg/dL.

Method of risk assessment: counting major risk factors and estimating 10-year CHD risk

Risk status in persons *without* clinically manifest CHD or other clinical forms of atherosclerotic disease is determined by a 2-step procedure.

First, the number of risk factors is counted (Table 3). Second, for persons with multiple (2+) risk factors, 10-year risk assessment is carried out with Framingham scoring (see Appendix) to identify individuals whose short-term (10-year) risk warrants consideration of intensive treatment. Estimation of the 10-year CHD risk adds a step to risk assessment beyond risk factor counting, but this step is warranted because it allows better targeting of intensive treatment to people who will benefit from it. When 0-1 risk factor is present, Framingham scoring is not necessary because 10-year risk rarely reaches levels for intensive intervention; a very high LDL level in such a person may nevertheless warrant consideration of drug therapy to reduce long-term risk. Risk factors used in Framingham scoring include age, total cholesterol, HDL cholesterol, blood pressure, and cigarette smoking. Total cholesterol is used for 10-year risk assessment because of a larger and more robust Framingham database for total than for LDL cholesterol, but LDL cholesterol is the primary target of therapy. Framingham scoring divides persons with multiple risk factors into those with 10-year risk for CHD of >20%, 10-20%, and <10%. It should be noted that this 2-step sequence can be reversed with essentially the same results.* Initial risk assessment in ATP III uses the major risk factors to define the core risk status. Only after the core risk status has been determined should any other risk modifiers be taken into consideration for adjusting the therapeutic approach.

Role of other risk factors in risk assessment

ATP III recognizes that risk for CHD is influenced by other factors not included among the major, independent risk factors (Table 3). Among these are *life-habit risk factors* and *emerging risk factors.* The former include obesity, physical inactivity, and atherogenic diet; the latter consist of lipoprotein (a), homocysteine, prothrombotic and proinflammatory factors, impaired fasting glucose, and evidence of subclinical atherosclerotic disease. The *life-habit risk factors* are direct targets for clinical intervention, but are not used to set a lower LDL cholesterol goal of therapy. The *emerging risk factors* do not categorically modify LDL cholesterol goals; however, they appear to contribute to CHD risk to varying degrees and can have utility in selected persons to guide intensity of risk-reduction therapy. Their presence can modulate clinical judgment when making therapeutic decisions.

Metabolic syndrome

Many persons have a constellation of major risk factors, life-habit risk factors, and emerging risk factors that constitute a condition called the

*If Framingham scoring is carried out *before* risk factor counting, persons with <10 percent risk are then divided into those with 2+ risk factors and 0-1 risk factor by risk factor counting to determine the appropriate LDL goal (see Table 4).

metabolic syndrome. Factors characteristic of the metabolic syndrome are abdominal obesity, atherogenic dyslipidemia (elevated triglyceride, small LDL particles, low HDL cholesterol), raised blood pressure, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states. ATP III recognizes the metabolic syndrome as a secondary target of risk-reduction therapy, after the primary target—LDL cholesterol. Diagnosis and treatment of the metabolic syndrome is described beginning on page 15 under "Benefit Beyond LDL Lowering: The Metabolic Syndrome as a Secondary Target of Therapy."

The link between risk assessment and cost effectiveness

In ATP III, a primary aim is to match intensity of LDL-lowering therapy with absolute risk. Everyone with elevated LDL cholesterol is treated with lifestyle changes that are effective in lowering LDL levels. Persons at relatively high risk are also candidates for drug treatment, which is very effective but entails significant additional expense. The cutpoints for drug treatment are based primarily on risk-benefit considerations: those at higher risk are likely to get greater benefit. However, cutpoints for recommended management based on therapeutic efficacy are checked against currently accepted standards for cost effectiveness. Lifestyle changes are the most cost-effective means to reduce risk for CHD. Even so, to achieve maximal benefit, many persons will require LDL-lowering drugs. Drug therapy is the major expense of LDL-lowering therapy, and it dominates cost-effectiveness analysis. However, the costs of LDL-lowering drugs are currently in flux and appear to be declining. This report recognizes that as drug prices decline it will be possible to extend drug use to lower risk persons and still be cost effective. In addition, ATP III recognizes that some persons with high long-term risk are candidates for LDL-lowering drugs even though use of drugs may not be cost effective by current standards.

Primary Prevention With LDL-Lowering Therapy

Primary prevention of CHD offers the greatest opportunity for reducing the burden of CHD in the United States. The clinical approach to primary prevention is founded on the public health approach that calls for lifestyle changes, including: 1) reduced intakes of saturated fat and cholesterol, 2) increased physical activity, and 3) weight control, to lower population cholesterol levels and reduce CHD risk, but the clinical approach intensifies preventive strategies for higher risk persons. One aim of primary prevention is to reduce long-term risk (>10 years) as well as short-term risk (≤10 years). LDL goals in primary prevention depend on a person's absolute risk for CHD (i.e., the probability of having a CHD

event in the short term or the long term)—the higher the risk, the lower the goal. Therapeutic lifestyle changes are the foundation of clinical primary prevention. Nonetheless, some persons at higher risk because of high or very high LDL cholesterol levels or because of multiple risk factors are candidates for LDL-lowering drugs. Recent primary prevention trials show that LDL-lowering drugs reduce risk for major coronary events and coronary death even in the short term.

Any person with elevated LDL cholesterol or other form of hyperlipidemia should undergo clinical or laboratory assessment to rule out secondary dyslipidemia before initiation of lipid-lowering therapy. Causes of secondary dyslipidemia include:

- Diabetes
- Hypothyroidism
- Obstructive liver disease
- Chronic renal failure
- Drugs that increase LDL cholesterol and decrease HDL cholesterol (progestins, anabolic steroids, and corticosteroids).

Once secondary causes have been excluded or, if appropriate, treated, the goals for LDL-lowering therapy in primary prevention are established according to a person's risk category (Table 4).

Secondary Prevention With LDL-Lowering Therapy

Recent clinical trials demonstrate that LDL-lowering therapy reduces total mortality, coronary mortality, major coronary events, coronary artery procedures, and stroke in persons with established CHD. As shown in Table 2, an LDL cholesterol level of <100 mg/dL is *optimal;* therefore, ATP III specifies an LDL cholesterol <100 mg/dL as the goal of therapy in secondary prevention. This goal is supported by clinical trials with both clinical and angiographic endpoints and by prospective epidemiological studies. The same goal should apply for persons with CHD risk equivalents. When persons are hospitalized for acute coronary syndromes or coronary procedures, lipid measures should be taken on admission or within 24 hours. These values can guide the physician on initiation of LDL-lowering therapy before or at discharge. Adjustment of therapy may be needed after 12 weeks.

LDL-Lowering Therapy in Three Risk Categories

The two major modalities of LDL-lowering therapy are *therapeutic lifestyle changes* (TLC) and *drug therapy.* Both are described in more detail later. The TLC Diet stresses reductions in saturated fat and cholesterol intakes. When the metabolic syndrome or its associated lipid risk factors (elevated

triglyceride or low HDL cholesterol) are present, TLC also stresses weight reduction and increased physical activity. Table 5 defines LDL cholesterol goals and cutpoints for initiation of TLC and for drug consideration for persons with three categories of risk: CHD and CHD risk equivalents; multiple (2+) risk factors (10-year risk 10-20% and <10%); and 0-1 risk factor.

Table 5: LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.

Risk Category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor†	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

* *Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.*

† *Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.*

CHD and CHD risk equivalents

For persons with CHD and CHD risk equivalents, LDL-lowering therapy greatly reduces risk for major coronary events and stroke and yields highly favorable cost-effectiveness ratios. The cut-points for initiating lifestyle and drug therapies are shown in Table 5.

- *If baseline LDL cholesterol is ≥130 mg/dL*, intensive lifestyle therapy and maximal control of other risk factors should be started. Moreover, for most patients, an LDL-lowering drug will be required to achieve an LDL cholesterol <100 mg/dL; thus an LDL cholesterol lowering drug can be started simultaneously with TLC to attain the goal of therapy.

- *If LDL cholesterol levels are 100-129 mg/dL*, either at baseline or on LDL-lowering therapy, several therapeutic approaches are available:

- Initiate or intensify lifestyle and/or drug therapies specifically to lower LDL.
- Emphasize weight reduction and increased physical activity in persons with the metabolic syndrome.
- Delay use or intensification of LDL-lowering therapies and institute treatment of other lipid or nonlipid risk factors; consider use of other lipid-modifying drugs (e.g., nicotinic acid or fibric acid) if the patient has elevated triglyceride or low HDL cholesterol.

- *If baseline LDL cholesterol is <100 mg/dL,* further LDL-lowering therapy is not required. Patients should nonetheless be advised to follow the TLC Diet on their own to help keep the LDL level optimal. Several clinical trials are currently underway to assess benefit of lowering LDL cholesterol to well below 100 mg/dL. At present, emphasis should be placed on controlling other lipid and nonlipid risk factors and on treatment of the metabolic syndrome, if present.

Multiple (2+) risk factors and 10-year risk ≤20%

For persons with multiple (2+) risk factors and 10-year risk ≤ 20%, intensity of therapy is adjusted according to 10-year risk and LDL cholesterol level. The treatment approach for each category is summarized in Table 5.

- *Multiple (2+) risk factors and a 10-year risk of 10-20%*. In this category, the goal for LDL cholesterol is <130 mg/dL. The therapeutic aim is to reduce short-term risk as well as long-term risk for CHD. If baseline LDL cholesterol is ≥130 mg/dL, TLC is initiated and maintained for 3 months. If LDL remains ≥130 mg/dL after 3 months of TLC, consideration can be given to starting an LDL-lowering drug to achieve the LDL goal of <130 mg/dL. Use of LDL-lowering drugs at this risk level reduces CHD risk and is cost-effective. If the LDL falls to less than 130 mg/dL on TLC alone, TLC can be continued without adding drugs. In older persons (≥65 years), clinical judgment is required for how intensively to apply these guidelines; a variety of factors, including concomitant illnesses, general health status, and social issues may influence treatment decisions and may suggest a more conservative approach.

- *Multiple (2+) risk factors and a 10-year risk of <10%*. In this category, the goal for LDL cholesterol also is <130 mg/dL. The therapeutic aim, however, is primarily to reduce longer-term risk. If baseline LDL cholesterol is ≥130 mg/dL, the TLC Diet is initiated to reduce LDL cholesterol. If LDL is <160 mg/dL on TLC alone, it should be continued. LDL-lowering drugs generally are not recommended because the patient is not at high short-term risk. On the other hand, if

LDL cholesterol is ≥160 mg/dL, drug therapy can be considered to achieve an LDL cholesterol <130 mg/dL; the primary aim is to reduce long-term risk. Cost-effectiveness is marginal, but drug therapy can be justified to slow development of coronary atherosclerosis and to reduce long-term risk for CHD.

Zero to one risk factor

Most persons with 0-1 risk factor have a 10-year risk <10%. They are managed according to Table 5. The goal for LDL cholesterol in this risk category is <160 mg/dL. The primary aim of therapy is to reduce long-term risk. First-line therapy is TLC. If after 3 months of TLC the LDL cholesterol is <160 mg/dL, TLC is continued. However, if LDL cholesterol is 160-189 mg/dL after an adequate trial of TLC, drug therapy is *optional* depending on clinical judgment. Factors favoring use of drugs include:

- A severe single risk factor (heavy cigarette smoking, poorly controlled hypertension, strong family history of premature CHD, or very low HDL cholesterol);
- Multiple life-habit risk factors and emerging risk factors (if measured);
- 10-year risk approaching 10% (if measured; see Appendix).

If LDL cholesterol is ≥190 mg/dL despite TLC, drug therapy should be considered to achieve the LDL goal of <160 mg/dL.

The purpose of using LDL-lowering drugs in persons with 0-1 risk factor and elevated LDL cholesterol (≥160 mg/dL) is to slow the development of coronary atherosclerosis, which will reduce long-term risk. This aim may conflict with cost-effectiveness considerations; thus, clinical judgment is required in selection of persons for drug therapy, although a strong case can be made for using drugs when LDL cholesterol is ≥190 mg/dL after TLC.

For persons whose LDL cholesterol levels are already below goal levels upon first encounter, instructions for appropriate changes in life habits, periodic followup, and control of other risk factors are needed.

Therapeutic Lifestyle Changes in LDL-Lowering Therapy

ATP III recommends a multifaceted lifestyle approach to reduce risk for CHD. This approach is designated *therapeutic lifestyle changes (TLC).* Its essential features are:

- Reduced intakes of saturated fats (<7% of total calories) and cholesterol (<200 mg per day) (see Table 6 for overall composition of the TLC Diet)
- Therapeutic options for enhancing LDL lowering such as plant stanols/sterols (2 g/day) and increased viscous (soluble) fiber (10-25 g/day)
- Weight reduction
- Increased physical activity

Table 6. Nutrient Composition of the TLC Diet

Nutrient	Recommended Intake
Saturated fat*	Less than 7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25-35% of total calories
Carbohydrate†	50-60% of total calories
Fiber	20-30 g/day
Protein	Approximately 15% of total calories
Cholesterol	Less than 200 mg/day
Total calories (energy)‡	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain

** Trans fatty acids are another LDL-raising fat that should be kept at a low intake.*
† Carbohydrate should be derived predominantly from foods rich in complex carbohydrates including grains, especially whole grains, fruits, and vegetables.
‡ Daily energy expenditure should include at least moderate physical activity (contributing approximately 200 Kcal per day).

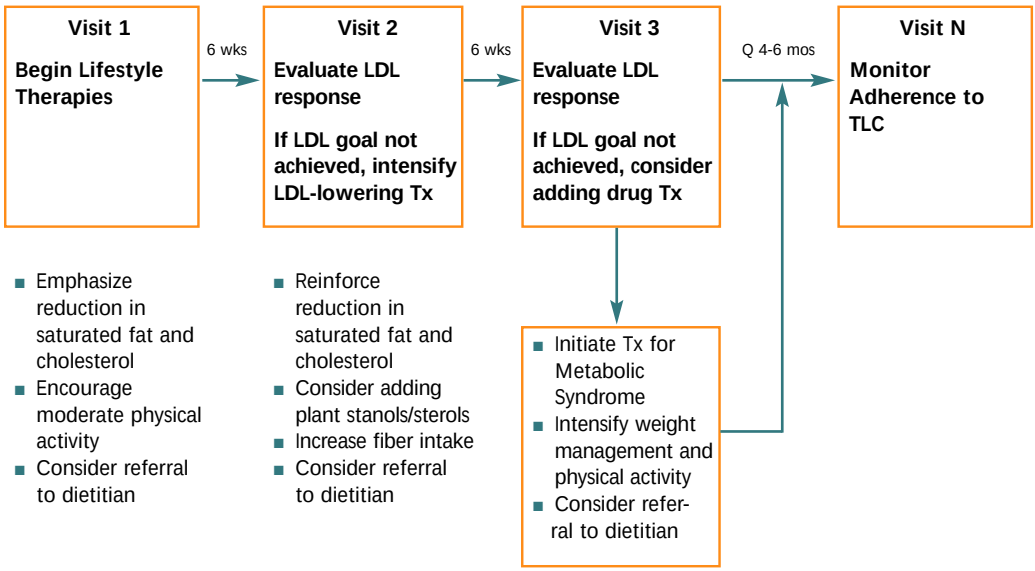
A model of steps in TLC is shown in Figure 1. To initiate TLC, intakes of saturated fats and cholesterol are reduced first to lower LDL cholesterol. To improve overall health, ATP III's TLC Diet generally contains the recommendations embodied in the Dietary Guidelines for Americans 2000. One exception is that total fat is allowed to range from 25-35% of total calories provided saturated fats and *trans* fatty acids are kept low. A higher intake of total fat, mostly in the form of unsaturated fat, can help to reduce triglycerides and raise HDL cholesterol in persons with the metabolic syndrome. In accordance with the Dietary Guidelines, moderate physical activity is encouraged. After 6 weeks, the LDL response is determined; if the LDL cholesterol goal has not been achieved, other therapeutic options for LDL lowering such as plant stanol/sterols and viscous fiber can be added.

After maximum reduction of LDL cholesterol with dietary therapy, emphasis shifts to management of the metabolic syndrome and associated lipid risk factors. The majority of persons with these latter abnormalities are overweight or obese and sedentary. Weight reduction therapy for overweight or obese patients will enhance LDL lowering and will provide other health benefits including modifying other lipid and nonlipid risk factors.

Assistance in the management of overweight and obese persons is provided by the *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults* from the NHLBI Obesity Education Initiative (1998). Additional risk reduction can be achieved by simultaneously increasing physical activity.

At all stages of dietary therapy, physicians are encouraged to refer patients to registered dietitians or other qualified nutritionists for *medical nutrition therapy,* which is the term for the nutritional intervention and guidance provided by a nutrition professional.

Figure 1. A Model of Steps in Therapeutic Lifestyle Changes (TLC)



Drug Therapy to Achieve LDL Cholesterol Goals

A portion of the population whose short-term or long-term risk for CHD is high will require LDL-lowering drugs in addition to TLC to reach the designated goal for LDL cholesterol (see Table 5). When drugs are prescribed, attention to TLC should always be maintained and reinforced. Currently available drugs that affect lipoprotein metabolism and their major characteristics are listed in Table 7.

Some cholesterol-lowering agents are currently available over-the-counter (OTC) (e.g., nicotinic acid), and manufacturers of several classes of LDL-lowering drugs (e.g., statins, bile acid sequestrants) have applied to the

Table 7. Drugs Affecting Lipoprotein Metabolism

Drug Class, Agents and Daily Doses	Lipid/Lipoprotein Effects		Side Effects	Contraindications	Clinical Trial Results
HMG CoA reductase inhibitors (statins)*	LDL HDL TG	↓18-55% ↑5-15% ↓7-30%	Myopathy Increased liver enzymes	Absolute: • Active or chronic liver disease Relative: • Concomitant use of certain drugs†	Reduced major coronary events, CHD deaths, need for coronary procedures, stroke, and total mortality
Bile acid Sequestrants‡	LDL HDL TG	↓15-30% ↑3-5% No change or increase	Gastrointestinal distress Constipation Decreased absorption of other drugs	Absolute: • dysbeta-lipoproteinemia • TG >400 mg/dL Relative: • TG >200 mg/dL	Reduced major coronary events and CHD deaths
Nicotinic acid¥	LDL HDL TG	↓ 5-25% ↑15-35% ↓20-50%	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity	Absolute: • Chronic liver disease • Severe gout Relative: • Diabetes • Hyperuricemia • Peptic ulcer disease	Reduced major coronary events, and possibly total mortality
Fibric acids§	LDL *(may be increased in patients with high TG)* HDL TG	↓5-20% ↑10-20% ↓20-50%	Dyspepsia Gallstones Myopathy Unexplained non-CHD deaths in WHO study	Absolute: • Severe renal disease • Severe hepatic disease	Reduced major coronary events

* *Lovastatin (20-80 mg), pravastatin (20-40 mg), simvastatin (20-80 mg), fluvastatin (20-80 mg), atorvastatin (10-80 mg), cerivastatin (0.4-0.8 mg).*

† *Cyclosporine, macrolide antibiotics, various antifungal agents and cytochrome P-450 inhibitors (fibrates and niacin should be used with appropriate caution).*

‡ *Cholestyramine (4-16 g), colestipol (5-20 g), colesevelam (2.6-3.8 g).*

¥ *Immediate release (crystalline) nicotinic acid (1.5-3 g), extended release nicotinic acid (Niaspan ®) (1-2 g), sustained release nicotinic acid (1-2 g).*

§ *Gemfibrozil (600 mg BID), fenofibrate (200 mg), clofibrate (1000 mg BID).*

Food and Drug Administration (FDA) to allow these agents to become OTC medications. At the time of publication of ATP III, the FDA has not granted permission for OTC status for statins or bile acid sequestrants. If an OTC cholesterol-lowering drug is or becomes available, patients should continue to consult with their physicians about whether to initiate drug treatment, about setting the goals of therapy, and about monitoring for therapeutic responses and side effects.

Secondary prevention: drug therapy for CHD and CHD risk equivalents

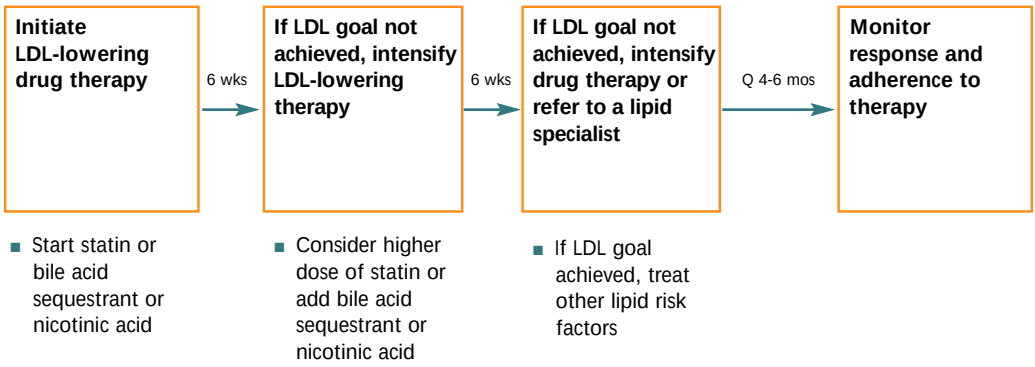
For persons with CHD and CHD risk equivalents, the goal is to attain an LDL cholesterol level <100 mg/dL. The cutpoints for initiating lifestyle and drug therapies are shown in Table 5, and the approach to treatment is discussed immediately after Table 5. Most CHD patients will need LDL-lowering drug therapy. Other lipid risk factors may also warrant consideration of drug treatment. Whether or not lipid-modifying drugs are used, nonlipid risk factors require attention and favorable modification.

In persons admitted to the hospital for a major coronary event, LDL cholesterol should be measured on admission or within 24 hours. This value can be used for treatment decisions. In general, persons hospitalized for a coronary event or procedure should be discharged on drug therapy if the LDL cholesterol is ≥130 mg/dL. If the LDL is 100–129 mg/dL, clinical judgment should be used in deciding whether to initiate drug treatment at discharge, recognizing that LDL cholesterol levels begin to decline in the first few hours after an event and are significantly decreased by 24-48 hours and may remain low for many weeks. Thus, the initial LDL cholesterol level obtained in the hospital may be substantially lower than is usual for the patient. Some authorities hold drug therapy should be initiated whenever a patient hospitalized for a CHD-related illness is found to have an LDL cholesterol >100 mg/dL. Initiation of drug therapy at the time of hospital discharge has two advantages. First, at that time patients are particularly motivated to undertake and adhere to risk-lowering interventions; and second, failure to initiate indicated therapy early is one of the causes of a large "treatment gap," because outpatient followup is often less consistent and more fragmented.

LDL-lowering drug therapy for primary prevention

Table 5 shows the cutpoints for considering drug treatment in primary prevention. The general approach to management of drug therapy for primary prevention is outlined in Figure 2.

Figure 2. Progression of Drug Therapy in Primary Prevention



When drug therapy for primary prevention is a consideration, the third visit of dietary therapy (see Figure 1) will typically be the visit to initiate drug treatment. Even if drug treatment is started, TLC should be continued. As with TLC, the first priority of drug therapy is to achieve the goal for LDL cholesterol. For this reason, an LDL-lowering drug should be started. The usual drug will be a statin, but alternatives are a bile acid sequestrant or nicotinic acid. In most cases, the statin should be started at a moderate dose. In many patients, the LDL cholesterol goal will be achieved, and higher doses will not be necessary. The patient's response should be checked about 6 weeks after starting drug therapy. If the goal of therapy has been achieved, the current dose can be maintained. However, if the goal has not been achieved, LDL-lowering therapy can be intensified, either by increasing the dose of statin or by combining a statin with a bile acid sequestrant or nicotinic acid.

After 12 weeks of drug therapy, the response to therapy should again be assessed. If the LDL cholesterol goal is still not achieved, consideration can be given to further intensification of drug therapy. If the LDL goal cannot be attained by standard lipid-lowering therapy, consideration should be given to seeking consultation from a lipid specialist. Once the goal for LDL cholesterol has been attained, attention can turn to other lipid risk factors and nonlipid factors. Thereafter, patients can be monitored for response to therapy every 4 to 6 months, or more often if considered necessary.

Benefit Beyond LDL Lowering: The Metabolic Syndrome as a Secondary Target of Therapy

Evidence is accumulating that risk for CHD can be reduced beyond LDL-lowering therapy by modification of other risk factors. One potential

secondary target of therapy is the metabolic syndrome, which represents a constellation of lipid and nonlipid risk factors of metabolic origin. This syndrome is closely linked to a generalized metabolic disorder called *insulin resistance* in which the normal actions of insulin are impaired. Excess body fat (particularly abdominal obesity) and physical inactivity promote the development of insulin resistance, but some individuals also are genetically predisposed to insulin resistance.

The risk factors of the metabolic syndrome are highly concordant; in aggregate they enhance risk for CHD at any given LDL cholesterol level. For purposes of ATP III, the diagnosis of the metabolic syndrome is made when three or more of the risk determinants shown in Table 8 are present. These determinants include a combination of categorical and borderline risk factors that can be readily measured in clinical practice.

Table 8. Clinical Identification of the Metabolic Syndrome

Risk Factor	Defining Level
Abdominal Obesity*	Waist Circumference†
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mmHg
Fasting glucose	≥110 mg/dL

* *Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated body mass index (BMI). Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.*

† *Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 94-102 cm (37-39 in). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.*

Management of the metabolic syndrome has a two-fold objective: (1) to reduce underlying causes (i.e., obesity and physical inactivity), and (2) to treat associated nonlipid and lipid risk factors.

Management of underlying causes of the metabolic syndrome

First-line therapies for all lipid and nonlipid risk factors associated with the metabolic syndrome are weight reduction and increased physical activity, which will effectively reduce all of these risk factors. Therefore, after

appropriate control of LDL cholesterol, TLC should stress weight reduction and physical activity if the metabolic syndrome is present.

Weight control. In ATP III overweight and obesity are recognized as major, underlying risk factors for CHD and identified as direct targets of intervention. Weight reduction will enhance LDL lowering and reduce all of the risk factors of the metabolic syndrome. The recommended approaches for reducing overweight and obesity are contained in the clinical guidelines of the NHLBI Obesity Education Initiative.

Physical activity. Physical inactivity is likewise a major, underlying risk factor for CHD. It augments the lipid and nonlipid risk factors of the metabolic syndrome. It further may enhance risk by impairing cardiovascular fitness and coronary blood flow. Regular physical activity reduces very low density lipoprotein (VLDL) levels, raises HDL cholesterol, and in some persons, lowers LDL levels. It also can lower blood pressure, reduce insulin resistance, and favorably influence cardiovascular function. Thus, ATP III recommends that regular physical activity become a routine component in management of high serum cholesterol. The evidence base for this recommendation is contained in the *U.S. Surgeon General's Report on Physical Activity.*

Specific Treatment of Lipid and Non-Lipid Risk Factors

Beyond the underlying risk factors, therapies directed against the lipid and nonlipid risk factors of the metabolic syndrome will reduce CHD risk. These include treatment of hypertension, use of aspirin in patients with CHD to reduce the prothrombotic state (guidelines for aspirin use in primary prevention have not been firmly established), and treatment of elevated triglycerides and low HDL cholesterol as discussed below under Management of Specific Dyslipidemias.

Special Issues

Management of Specific Dyslipidemias

Very high LDL cholesterol (≥190 mg/dL). Persons with very high LDL cholesterol usually have genetic forms of hypercholesterolemia: monogenic familial hypercholesterolemia, familial defective apolipoprotein B, and polygenic hypercholesterolemia. Early detection of these disorders through cholesterol testing in young adults is needed to prevent premature CHD. Family testing is important to identify similarly affected relatives. These

disorders often require combined drug therapy (statin + bile acid sequestrant) to achieve the goals of LDL-lowering therapy.

Elevated serum triglycerides. Recent meta-analyses of prospective studies indicate that elevated triglycerides are also an independent risk factor for CHD. Factors contributing to elevated (higher than normal) triglycerides in the general population include: obesity and overweight, physical inactivity, cigarette smoking, excess alcohol intake, high carbohydrate diets (>60% of energy intake), several diseases (e.g., type 2 diabetes, chronic renal failure, nephrotic syndrome), certain drugs (e.g., corticosteroids, estrogens, retinoids, higher doses of beta-adrenergic blocking agents), and genetic disorders (familial combined hyperlipidemia, familial hypertriglyceridemia, and familial dysbetalipoproteinemia).

In clinical practice, elevated serum triglycerides are most often observed in persons with the metabolic syndrome, although secondary or genetic factors can heighten triglyceride levels. ATP III adopts the following classification of serum triglycerides:

- Normal triglycerides: <150 mg/dL
- Borderline-high triglycerides: 150-199 mg/dL
- High triglycerides: 200-499 mg/dL
- Very high triglycerides: ≥500 mg/dL

The finding that elevated triglycerides are an independent CHD risk factor suggests that some triglyceride-rich lipoproteins are atherogenic. The latter are partially degraded VLDL, commonly called *remnant lipoproteins.* In clinical practice, VLDL cholesterol is the most readily available measure of atherogenic remnant lipoproteins. Thus, VLDL cholesterol can be a target of cholesterol-lowering therapy. ATP III identifies the sum of LDL+VLDL cholesterol [termed *non-HDL cholesterol* (total cholesterol minus HDL cholesterol)] as a secondary target of therapy in persons with high triglycerides (≥200 mg/dL). The goal for non-HDL cholesterol in persons with high serum triglycerides can be set at 30 mg/dL higher than that for LDL cholesterol (Table 9) on the premise that a VLDL cholesterol level ≤30 mg/dL is normal.

The treatment strategy for elevated triglycerides depends on the causes of the elevation and its severity. For all persons with elevated triglycerides, the primary aim of therapy is to achieve the target goal for LDL cholesterol. When triglycerides are *borderline high* (150-199 mg/dL), emphasis should also be placed on weight reduction and increased physical activity. For *high triglycerides* (200-499 mg/dL), non-HDL cholesterol becomes a secondary

Table 9. Comparison of LDL Cholesterol and Non-HDL Cholesterol Goals for Three Risk Categories

Risk Category	LDL Goal (mg/dL)	Non-HDL-C Goal (mg/dL)
CHD and CHD Risk Equivalent (10-year risk for CHD >20%)	<100	<130
Multiple (2+) Risk Factors and 10-year risk ≤20%	<130	<160
0-1 Risk Factor	<160	<190

target of therapy. Aside from weight reduction and increased physical activity, drug therapy can be considered in high-risk persons to achieve the non-HDL cholesterol goal. There are two approaches to drug therapy. First, the non-HDL cholesterol goal can be achieved by intensifying therapy with an LDL-lowering drug; or second, nicotinic acid or fibrate can be added, if used with appropriate caution, to achieve the non-HDL cholesterol goal by further lowering of VLDL cholesterol. In rare cases in which triglycerides are *very high* (≥500 mg/dL), the initial aim of therapy is to prevent acute pancreatitis through triglyceride lowering. This approach requires very low fat diets (≤15% of calorie intake), weight reduction, increased physical activity, and usually a triglyceride-lowering drug (fibrate or nicotinic acid). Only after triglyceride levels have been lowered to <500 mg/dL should attention turn to LDL lowering to reduce risk for CHD.

Low HDL cholesterol. Low HDL cholesterol is a strong independent predictor of CHD. In ATP III, low HDL cholesterol is defined categorically as a level <40 mg/dL, a change from the level of <35 mg/dL in ATP II. In the present guidelines, low HDL cholesterol both modifies the goal for LDL-lowering therapy and is used as a risk factor to estimate 10-year risk for CHD.

Low HDL cholesterol levels have several causes, many of which are associated with insulin resistance, i.e., elevated triglycerides, overweight and obesity, physical inactivity, and type 2 diabetes. Other causes are cigarette smoking, very high carbohydrate intakes (>60% of calories), and certain drugs (e.g., beta-blockers, anabolic steroids, progestational agents)

ATP III does not specify a goal for HDL raising. Although clinical trial results suggest that raising HDL will reduce risk, the evidence is insufficient to specify a goal of therapy. Furthermore, currently available drugs do not robustly raise HDL cholesterol. Nonetheless, a low HDL should receive clinical attention and management according to the following sequence. In all persons with low HDL cholesterol, the primary target of therapy is LDL

cholesterol; ATP III guidelines should be followed to achieve the LDL cholesterol goal. Second, after the LDL goal has been reached, emphasis shifts to weight reduction and increased physical activity (when the metabolic syndrome is present). When a low HDL cholesterol is associated with high triglycerides (200-499 mg/dL), secondary priority goes to achieving the non-HDL cholesterol goal, as outlined before. Also, if triglycerides are <200 mg/dL (isolated low HDL cholesterol), drugs for HDL raising (fibrates or nicotinic acid) can be considered; however, treatment for isolated low HDL is mostly reserved for persons with CHD and CHD risk equivalents.

Diabetic dyslipidemia. This disorder is essentially atherogenic dyslipidemia (high triglycerides, low HDL, and small dense LDL) in persons with type 2 diabetes. Although elevated triglycerides and/or low HDL cholesterol are common in persons with diabetes, clinical trial results support the identification of LDL cholesterol as the primary target of therapy, as it is in those without diabetes. Since diabetes is designated a CHD risk equivalent in ATP III, the LDL cholesterol goal of therapy for most persons with diabetes will be <100 mg/dL. Furthermore, when LDL cholesterol is ≥130 mg/dL, most persons with diabetes will require initiation of LDL-lowering drugs simultaneously with TLC to achieve the LDL goal. When LDL cholesterol levels are in the range of 100-129 mg/dL at baseline or on treatment, several therapeutic options are available: increasing intensity of LDL-lowering therapy, adding a drug to modify atherogenic dyslipidemia (fibrate or nicotinic acid), or intensifying control of other risk factors including hyperglycemia. When triglyceride levels are ≥200 mg/dL, non-HDL cholesterol becomes a secondary target of cholesterol-lowering therapy. Several ongoing clinical trials (e.g., Antihypertensive and Lipid Lowering Heart Attack Trial [ALLHAT]) will better quantify the magnitude of the benefit of LDL-lowering treatment in older individuals with diabetes. In older persons (≥65 years of age) with diabetes but no additional CHD risk factors other than age, clinical judgment is required for how intensively to apply these guidelines; a variety of factors, including concomitant illnesses, general health status, and social issues may influence treatment decisions and may suggest a more conservative approach.

Special Considerations for Different Population Groups

Middle-aged men (35-65 years). In general, men have a higher risk for CHD than do women. Middle-aged men in particular have a high prevalence of the major risk factors and are predisposed to abdominal obesity and the metabolic syndrome. A sizable fraction of all CHD in men occurs in middle age. Thus, many middle-aged men carry a relatively high risk for CHD, and for those who do, intensive LDL-lowering therapy is needed.

Women (ages 45-75 years). In women, onset of CHD generally is delayed by some 10-15 years compared with that in men; thus most CHD in women occurs after age 65. All risk factors contribute to CHD in women, and most premature CHD in women (<65 years) occurs in those with multiple risk factors and the metabolic syndrome. Despite the previous belief that the gender difference in risk for CHD reflects a protective effect of estrogen in women, recent secondary and primary prevention trials cast doubt on the use of hormone replacement therapy to reduce CHD risk in postmenopausal women. In contrast, the favorable effects of statin therapy in women in clinical trials make a cholesterol-lowering drug preferable to hormone replacement therapy for CHD risk reduction. Women should be treated similarly to men for secondary prevention. For primary prevention, ATP III's general approach is similarly applicable for women and men. However, the later onset of CHD for women in general should be factored into clinical decisions about use of cholesterol-lowering drugs.

Older adults (men ≥ 65 years and women ≥ 75 years). Overall, most new CHD events and most coronary deaths occur in older persons (≥ 65 years). A high level of LDL cholesterol and low HDL cholesterol still carry predictive power for the development of CHD in older persons. Nevertheless, the finding of advanced subclinical atherosclerosis by noninvasive testing can be helpful for confirming the presence of high risk in older persons. Secondary prevention trials with statins have included a sizable number of older persons, mostly in the age range of 65 to 75 years. In these trials, older persons showed significant risk reduction with statin therapy. Thus, no hard-and-fast age restrictions appear necessary when selecting persons with established CHD for LDL-lowering therapy. For primary prevention, TLC is the first line of therapy for older persons. However, LDL-lowering drugs can also be considered when older persons are at higher risk because of multiple risk factors or advanced subclinical atherosclerosis.

Younger adults (men 20-35 years; women 20-45 years). CHD is rare except in those with severe risk factors, e.g., familial hypercholesterolemia, heavy cigarette smoking, or diabetes. Even though clinical CHD is relatively rare in young adults, coronary atherosclerosis in its early stages may progress rapidly. The rate of development of coronary atherosclerosis earlier in life correlates with the major risk factors. In particular, long-term prospective studies reveal that elevated serum cholesterol detected in young adulthood predicts a higher rate of premature CHD in middle age. Thus, risk factor identification in young adults is an important aim for long-term prevention. The combination of early detection and early intervention on elevated LDL cholesterol with life-habit changes offers the opportunity for delaying or preventing onset of CHD later in life. For young adults with LDL cholesterol levels ≥130 mg/dL, TLC should be instituted and emphasized.

Particular attention should be given to young men who smoke and have a high LDL cholesterol (160-189 mg/dL); they may be candidates for LDL-lowering drugs. When young adults have very high LDL cholesterol levels (≥190 mg/dL), drug therapy should be considered, as in other adults. Those with severe genetic forms of hypercholesterolemia may require LDL-lowering drugs in combination (e.g., statin + bile acid sequestrant).

Racial and ethnic groups. African Americans have the highest overall CHD mortality rate and the highest out-of-hospital coronary death rates of any ethnic group in the United States, particularly at younger ages. Although the reasons for the excess CHD mortality among African Americans have not been fully elucidated, it can be accounted for, at least in part, by the high prevalence of coronary risk factors. Hypertension, left ventricular hypertrophy, diabetes mellitus, cigarette smoking, obesity, physical inactivity, and multiple CHD risk factors all occur more frequently in African Americans than in whites. Other ethnic groups and minority populations in the United States include Hispanics, Native Americans, Asian and Pacific Islanders, and South Asians. Although limited data suggest that racial and ethnic groups vary somewhat in baseline risk for CHD, this evidence did not appear sufficient to lead the ATP III panel to modify general recommendations for cholesterol management in these populations.

Adherence to LDL-Lowering Therapy

Adherence to the ATP III guidelines by both patients and providers is a key to approximating the magnitude of the benefits demonstrated in clinical trials of cholesterol lowering. Adherence issues have to be addressed in order to attain the highest possible levels of CHD risk reduction. Thus, ATP III recommends the use of state-of-the-art multidisciplinary methods targeting the patient, providers, and health delivery systems to achieve the full population effectiveness of the guidelines for primary and secondary prevention (Table 10).

Table 10. Interventions to Improve Adherence

Focus on the Patient

- Simplify medication regimens
- Provide explicit patient instruction and use good counseling techniques to teach the patient how to follow the prescribed treatment
- Encourage the use of prompts to help patients remember treatment regimens
- Use systems to reinforce adherence and maintain contact with the patient
- Encourage the support of family and friends
- Reinforce and reward adherence
- Increase visits for patients unable to achieve treatment goal
- Increase the convenience and access to care
- Involve patients in their care through self-monitoring

Focus on the Physician and Medical Office

- Teach physicians to implement lipid treatment guidelines
- Use reminders to prompt physicians to attend to lipid management
- Identify a patient advocate in the office to help deliver or prompt care
- Use patients to prompt preventive care
- Develop a standardized treatment plan to structure care
- Use feedback from past performance to foster change in future care
- Remind patients of appointments and follow-up missed appointments

Focus on the Health Delivery System

- Provide lipid management through a lipid clinic
- Utilize case management by nurses
- Deploy telemedicine
- Utilize the collaborative care of pharmacists
- Execute critical care pathways in hospitals

Appendix

Shared Features of ATP III and ATP II

ATP III shares a set of core features with ATP II. These are shown in Table A.

Table A. Shared Features of ATP III and ATP II

- Continued identification of LDL cholesterol lowering as the primary goal of therapy
- Consideration of high LDL cholesterol (≥160 mg/dL) as a potential target for LDL-lowering drug therapy, specifically as follows:
  - For persons with multiple risk factors whose LDL levels are high (≥160 mg/dL) after dietary therapy, consideration of drug therapy is recommended
  - For persons with 0-1 risk factor, consideration of drug therapy (after dietary therapy) is optional for LDL 160-189 mg/dL and recommended for LDL ≥190 mg/dL
- Emphasis on intensive LDL-lowering therapy in persons with established CHD
- Identification of three categories of risk for different LDL goals and different intensities of LDL-lowering therapy:
  - CHD and CHD risk equivalents* (other forms of clinical atherosclerotic disease)
  - Multiple (2+) risk factors†
  - 0-1 risk factor
- Identification of subpopulations, besides middle-aged men, for detection of high LDL cholesterol (and other lipid risk factors) and for clinical intervention. These include:
  - Young adults
  - Postmenopausal women
  - Older persons
- Emphasis on weight loss and physical activity to enhance risk reduction in persons with elevated LDL cholesterol

* *A CHD risk equivalent is a condition that carries an absolute risk for developing new CHD equal to the risk for having recurrent CHD events in persons with established CHD.*

† *Risk factors that continue to modify the LDL goal include cigarette smoking, hypertension, low HDL cholesterol, family history of premature CHD, age (male ≥45 years and female ≥55 years), and diabetes (in ATP III diabetes is regarded as a CHD risk equivalent).*

Estimating 10-Year Risk for Men and Women

Risk assessment for determining the 10-year risk for developing CHD is carried out using Framingham risk scoring (Table B1 for men and Table B2 for women). The risk factors included in the Framingham calculation of 10-year risk are: age, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, and cigarette smoking. The first step is to calculate the number of points for each risk factor. For initial assessment, values for total cholesterol and HDL cholesterol are required. Because of a larger database, Framingham estimates are more robust for total cholesterol than for LDL cholesterol. Note, however, that the LDL cholesterol level remains the primary target of therapy. Total cholesterol and HDL cholesterol values should be the average of at least two measurements obtained from lipoprotein analysis. The blood pressure value used is that obtained at the time of assessment, regardless of whether the person is on anti-hypertensive therapy. However, if the person is on antihypertensive treatment, an extra point is added beyond points for the blood pressure reading because treated hypertension carries residual risk (see Tables B1 and B2). The average of several blood pressure measurements, as recommended by the Joint National Committee (JNC), is needed for an accurate measure of baseline blood pressure. The designation “smoker” means any cigarette smoking in the past month. The total risk score sums the points for each risk factor. The 10-year risk for myocardial infarction and coronary death (hard CHD) is estimated from total points, and the person is categorized according to absolute 10-year risk as indicated above (see Table 5).

Table B1. Estimate of 10-Year Risk for Men (Framingham Point Scores)

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Total Cholesterol	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Point Total	10-Year Risk %
<0	< 1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥17	≥ 30

Table B2. Estimate of 10-Year Risk for Women (Framingham Point Scores)

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Total Cholesterol	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
≥280	13	10	7	4	2

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

Point Total	10-Year Risk %
<9	< 1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥ 30

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Public Health Service
National Institutes of Health
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May 2001

Cohen DE, Anania FA, and Chalasani N. An Assessment of Statin Safety by Hepatologists. *Am J Cardiol 2006*; 97[suppl]:77C-81C.

McKenney JM, Davidson MH, et al. Final Conclusions and Recommendations of the National Lipid Association Statin Safety Assessment Task Force. *Am J Cardiol* 2006;97[suppl]:89C-94C.

The United States FDA has the following definitions for the pregnancy categories:

United States FDA Pharmaceutical Pregnancy Categories	
Pregnancy Category A	Adequate and well-controlled studies have failed to demonstrate a risk to the foetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
Pregnancy Category B	Animal reproduction studies have failed to demonstrate a risk to the foetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies which have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the foetus in any trimester.
Pregnancy Category C	Animal reproduction studies have shown an adverse effect on the foetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Pregnancy Category D	There is positive evidence of human foetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Pregnancy Category X	Studies in animals or humans have demonstrated foetal abnormalities and/or there is positive evidence of human foetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

One characteristic of the FDA definitions of the pregnancy categories is that the FDA requires a relatively large amount of high-quality data on a pharmaceutical for it to be defined as Pregnancy Category A. As a result of this, many drugs that would be considered Pregnancy Category A in other countries are allocated to Category C by the FDA.

Medical Team Leader Review of Non-prescription Mevacor® 20 mg New Drug Application

NDA #:	21-213
Sponsor:	Merck and Company Johnson & Johnson Merck Consumer Pharmaceuticals Co.
Date of Advisory Committee Meeting:	January 13 and 14, 2005
Clinical Reviewer:	Mary H. Parks, MD Deputy Division Director Division of Metabolic and Endocrine Drug Products

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I. BACKGROUND

I. A. History of Nonprescription Treatment of Hypercholesterolemia

Over-the-counter (OTC) management of hypercholesterolemia to reduce cardiovascular risk was first proposed in the mid-1990s, in applications to switch bile-acid binding resins from prescription-only to OTC dispensing. Advisory committee meetings were held in 1995 and again in 1997. No approvals were granted. As a result of the recommendations made by the Advisory Committees, the FDA issued a Guidance to Industry on Over-the-Counter Treatment of Hypercholesterolemia in 1997. In this document, hypercholesterolemia, a chronic, asymptomatic, metabolic derangement of multiple primary etiologies, was deemed a condition that required both accurate diagnosis, risk assessment, and, potentially, clinical testing as part of long-term follow up in the prevention of atherosclerotic cardiovascular disease. It was concluded that the medical management of this condition should be under the direction of a healthcare professional. This conclusion, therefore, precluded consideration of lipid-altering drugs as nonprescription drug products.

In July 2000, separate joint advisory committee meetings were held to discuss applications for the prescription to non-prescription (Rx-to-OTC) switches of two statins, lovastatin and pravastatin. Both sponsoring companies proposed a single, fixed dose of 10 mg as safe and effective for patients without clinically evident heart disease but who were at risk because of mildly elevated Total-C (200-240 mg/dL) and LDL-C (> 130 mg/dL). The Advisory Committee members recommended that both applications not be approved based on concerns of inadequate effectiveness (lipid altering and thus CV risk reduction) of the products and about safe and appropriate self-management of hypercholesterolemia given the data suggesting poor consumer comprehension of labeling.

In October 2000, the FDA took a "Not Approved" action on Merck's application, stating that "*neither the rationale for treating the proposed target population with Mevacor 10 mg in the over-the-counter (OTC) setting, nor a favorable benefit/risk ratio for such treatment has been adequately established. Furthermore, the ability of consumers to appropriately self-select and to adequately comply with chronic Mevacor therapy without the intervention of a physician has not been demonstrated*". Specific deficiencies of the application were also outlined in the letter and can be briefly summarized as follows:

- Current National Cholesterol Education Program (NCEP) Guidelines were not incorporated in the OTC treatment paradigm
- Inadequate information was provided, specifically regarding the Mevacor 10 mg dose and the proposed OTC target population, to support an expectation of a clinical benefit for Mevacor based on extrapolation from the clinical outcomes study, Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)
- The OTC study program had not included a cholesterol treatment goal, did not evaluate whether consumers would comprehend the importance of a treatment goal, and did not address whether consumers would make appropriate decisions in the event of not achieving that treatment goal
- The clinical and actual use studies failed to demonstrate that consumers understood the complexities of treating a chronic medical condition such as hypercholesterolemia. Specifically, assessment of individual CV risk, compliance, and adherence to chronic lovastatin therapy were deficiencies noted in the review of these trials.

- The program did not explain how a consumer can use an over-the-counter product whose prescription label recommends hepatic transaminase monitoring. In addition, the program did not demonstrate an ability of consumers to comprehend the risk of serious muscle toxicity associated with Mevacor therapy.
- Lovastatin is extensively metabolized by cytochrome P450 3A4 and many drugs may interfere with the metabolism of Mevacor OTC which would increase the risk for serious muscle toxicity. The OTC program did not demonstrate that consumers would understand the importance of drug-drug interactions.
- Post-approval consumer education programs and materials were not adequately tested. Information on the availability of accurate cholesterol testing in the OTC setting to allow informed selection and monitoring of therapy by consumers was not adequately provided in the NDA.
- Lovastatin is labeled Pregnancy Category X (not to be used in pregnancy). Given that Mevacor OTC was likewise proposed to be contraindicated in pregnancy, label comprehension in this regard as well as the actual potential of such use was not assessed. Additional postnatal development studies in animals (modeling human fetal neurological development) were recommended to shed further light on risks to the fetus of *in utero* lovastatin exposure.

Despite the non-approval recommendation, the Agency recognized that public interest in the availability of safe and effective therapies to treat hypercholesterolemia warranted interactions between Industry and the Agency to evaluate the feasibility of such therapies as nonprescription products. In order to formally re-open such discussion, in 2001, the Agency withdrew the 1997 Guidance to Industry. Over the past four years, meetings and formal and informal communication have occurred between members of the Division of Metabolic and Endocrine Drug Products (DMEDP) and Division of Over-the-Counter Drug Products (DOTCDP) and representatives of Merck.

I. B. New Guidelines for the Management of Hypercholesterolemia

Shortly after the action letter for NDA 21-213 was issued, the National Cholesterol Education Program (NCEP) published its third Executive Summary on the management of hyperlipidemia in adults (Adult Treatment Panel III or ATP III)[1] and promulgated new treatment guidelines. While a detailed discussion of these recommendations is beyond the scope of this briefing document, several new features of the NCEP Guidelines are relevant to the review of RX-to-OTC lovastatin switch.

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 CV event over a 10-year period. ATP-III uses Framingham point scores in estimating these 10-year CHD risks, with age, total-C, smoking status, HDL-C, and blood pressure contributing to the total score. These 10-yr CHD risk estimates determine whether an individual falls into one of 4 categories:

- CHD or CHD risk equivalents (10-yr risk > 20%)
- 2+ risk factors for heart disease (10-yr risk 10-20%)
- 2+ risk factors for heart disease (10-yr risk < 10%)
- none to 1 risk factor for heart disease

[1] Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001; 285(19):2486-2497.

Individuals with diabetes but without clinically evident CHD and those with other clinical forms of atherosclerotic disease (e.g., peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease) have equivalent status to those individuals with established CHD. Risk factors for heart disease that may modify LDL-C goals include smoking, HTN, HDL < 40 mg/dL, family history of premature CHD, and age.

While an over-simplification of the NCEP ATP-III publication, the following table summarizes the treatment approach for hypercholesterolemia.

Table 1. LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories as Summarized in the 2001 NCEP Guidelines for the Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Risk Category	LDL Goal (mg/dL)	LDL Level at which to initiate TLC (mg/dL)	LDL-C level at which to consider drug therapy (mg/dL)
CHD or CHD risk* equivalents (10-yr risk > 20%)	< 100	≥ 100	≥ 130 (100-129; drug optional)
2+ risk factors (10-yr risk ≤ 20%	< 130	≥130	10-yr risk 10-20%: ≥ 130
	< 130	≥ 130	10-yr risk <10%: ≥ 160
0-1 risk factor (10-yr risk < 10%)	160	≥ 160	≥ 190 (160-189:LDL-lowering drug optional)

*recent clinical trial data have resulted in recommendations for more aggressive LDL-lowering to < 70 mg/dL for patients at very high risk for a CV event

The NCEP ATP-III Guidelines also identified other lipid parameters beyond LDL-C that contributed to the atherosclerotic process that required treatment intervention if abnormal. Specifically, elevated serum triglyceride (TG) levels may contribute to risk for CHD, and the optimal level should be < 150 mg/dL. In patients who have reached their LDL-C goal but whose TGs were > 200 mg/dL, a secondary target of therapy is non-HDL-C (this comprises the pool of atherogenic, cholesterol-ester containing, apo B lipoproteins) with the goal being set 30 mg/dL higher than that for LDL-C. In many instances, this secondary target of therapy must be addressed with additional lipid-altering therapies (e.g., fibrates, niacin). Table 2 summarizes LDL-C and non-HDL-C goals of therapy by risk category.

Table 2. LDL-C and Non-HDL-C Goals for the 3 Risk Categories based on NCEP ATP-III

Risk Category	LDL Goal (mg/dL)	Non-HDL Goal (mg/dL)
CHD and CHD risk equivalent	< 100	< 130
2+ risk factors	< 130	< 160
0-1 risk factor	< 160	< 190

In July 2004, members of the Coordinating Committee of the National Cholesterol Education Program published updates to NCEP ATP-III based on the results of 5 major clinical outcomes trials published after May 2001.[2] These revised recommendations stated that in individuals with very high risk for a CV event, an LDL-C goal of < 70 mg/dL is a therapeutic option.

Based on these NCEP Guidelines and their recent updates, it is evident that the treatment approach for elevated cholesterol levels is complex, requiring more than just knowing one's cholesterol level. It should be anticipated that as additional data are available from clinical trials, as new information on risk factors and risk-factor management emerges, and as new therapeutic alternatives come to the fore, treatment recommendations are more than likely to be modified. Furthermore, the extent to which a given, single-drug, fixed-dose OTC treatment model adequately addresses current clinical goals of and/or can be adapted to this complex and changing area of medical management must be carefully considered.

II. PROPOSED OTC-ELIGIBLE PATIENT POPULATION AND LOVASATIN DOSE

The applicant identified the OTC-eligible population as being:

"*a primary prevention population with ≥2 risk factors and a ≤20% risk of CHD over 10 years without underlying chronic conditions that complicate consumer self-management.*"

The applicant further states that individuals with liver disease, LDL-C > 170 mg/dL, the metabolic syndrome, diabetes, CHD, a history of stroke or other atherosclerotic cardiac disease are not candidates for OTC lovastatin. These patients were excluded from nonprescription lovastatin use because their 10-yr CHD risk would unlikely be adequately treated with lovastatin 20 mg and more aggressive management of other risk factors would require direct physician management.

Consumers are considered eligible for nonprescription lovastatin if they meet the following criteria on the product label:

1. males 45 yrs or older or females 55 years or older; and
2. LDL-C between 130 and 170 mg/dL; and
3. having at least one of the following risk factors
   - smoking

[2] Grundy SM et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation*. 2004; 110:227-239.

- HDL-C between 1 and 39 mg/dL
- family history of heart attack in father/brother before age 55 or mother/sister before age 65
- high blood pressure

The Mevacor OTC-eligible patient population therefore corresponds with those individuals who are at intermediate risk for a CV event over 10 years (highlighted yellow in Table 1). Based on NCEP ATP III guidelines, LDL-C goal for the OTC-eligible population is < 130 mg/dL. Drug therapy should be considered after therapeutic lifestyle changes fail to achieve this goal (or < 160 mg/dL if 10-yr risk is < 10%).

In the original NDA submission for nonprescription lovastatin, the applicant proposed to market the 10 mg dose for OTC use. This dose was studied in a clinical efficacy study in the initial NDA submission and an average LDL-C reduction of 18% was observed in a population with a mean LDL-C of 143 mg/dL. Consequently, the LDL-lowering efficacy at this dose was thought to be inadequate for the current proposed OTC population. Furthermore, no data on clinical benefit were available at that dose.

In this resubmission, the sponsor has proposed a fixed daily dose of lovastatin 20 mg for nonprescription use.

III. CLINICAL DATA SUBMITTED IN SUPPORT OF NDA

The only new studies conducted for this NDA resubmission were a label comprehension study and a consumer use study. The label comprehension study was conducted after a series of pilot studies was conducted. The label that was evaluated in the label comprehension study was also studied in the consumer use study, Protocol 084 (CUSTOM), which was in progress when the label comprehension study began. Both of these studies were reviewed in detail by the Division of Over-the-Counter Drug Products with separate reviews provided in this briefing document.

The applicant has also summarized data from studies submitted to the NDA for prescription lovastatin and studies previously reviewed under the original NDA submission for non-prescription lovastatin 10 mg. In addition, worldwide marketing safety data and selected reviews of published literature on lovastatin are provided with this submission.

III. A. Efficacy Data

A significant portion of the efficacy data for nonprescription lovastatin relies on 2 controlled studies: the Expanded Clinical Experience with Lovastatin (EXCEL) and Air Force/Texas Coronary Atherosclerosis Project (AFCAPS/TexCAPS). These studies were submitted and reviewed as efficacy supplements to the prescription NDA and their data are already in the product label. This briefing document will only highlight the efficacy findings from these two studies and comment on what relevance they have for nonprescription lovastatin use.

III. B. Safety Data

The safety concerns associated with lovastatin that were outlined in the non-approval letter included muscle toxicity with drug-drug interactions representing an increased risk for muscle toxicity, increases in hepatic transaminases and Rx recommendations for clinical laboratory monitoring, and pregnancy category X labeling. The applicant has addressed two of these safety concerns by submitting data to the prescription NDA.

Preclinical/reproductive and toxicology data were submitted under supplement 061 to NDA 19-643 and reviewed by Dr. Karen Davis-Bruno. Her review of the data and the Agency's recommendation on pregnancy category X labeling are discussed in separate documents included in this briefing package. On October 18, 2004, the representatives of Merck and Company met with the Agency and were informed that based on review of the data submitted, with input from members of the FDA's Reprotoxicology Subcommittee, there is a "theoretical and demonstrated animal risk" with lovastatin. In view of the minimal benefit of continued use of lovastatin therapy during pregnancy, and the applicant's intention to maintain a contraindication for use during pregnancy, the prescription product label will retain its Pregnancy Category X labeling. For purposes of nonprescription lovastatin use, the Agency noted that OTC labels do not currently have a pregnancy category designation but carry language that would advise women on the safe use or avoidance of the product during pregnancy. As prescription labeling for lovastatin will remain Pregnancy Category X and contraindicated in pregnant women, the safety of nonprescription lovastatin would require the demonstration that females of childbearing potential or who are pregnant comprehend the product label and appropriately select or de-select to avoid any risk to the fetus.

The second safety concern that was addressed as a supplement to the prescription NDA was hepatic enzyme elevations and recommendations in the prescription labeling that patients have baseline and periodic monitoring of hepatic transaminases while taking lovastatin. No new studies were conducted by the applicant to support changes to the prescription labeling. However, the applicant referenced safety data from EXCEL, AFCAPS/TexCAPS, the Heart Protection Study which evaluated a similar HMG-CoA reductase inhibitor (simvastatin), worldwide safety reports, and published literature. This supplement was submitted to the Agency in July 2004 and is currently under review; however, this briefing document will provide an overview of the applicant's rationale for relying on these data to modify recommendations to the prescription labeling.

IV. CLINICAL EFFICACY

IV. A. Lipid-Altering Efficacy

Lipid-altering efficacy of lovastatin 20 mg is summarized from 3 different clinical sources: EXCEL, AFCAPS/TexCAPS, and CUSTOM. These three studies involved different patient populations, study designs, and treatment approaches. Consequently, differences in efficacy are not unexpected. The following table highlights relevant baseline features of the three study cohorts.

Table 3. Selected Baseline Characteristics of EXCEL, AFCAPS/TexCAPS and CUSTOM Cohorts

	EXCEL N=8245	**AFCAPS/TexCAPS N=6605**	**CUSTOM N=1061**
Gender male female	 4855 (58.9%) 3390 (41.1%)	 5608 (84.9%) 997 (15.1%)	 631 (59.5%) 430 (40.5%)
Age, yrs mean ± SD	 male 53.9 ± 10.4 female 58.4 ± 7.8	 all 58 ± 7	 all 56.5 ± 11.03

range	21-75	45-73	23-87 female 23-86
Mean Lipid Profile, mg/dL LDL TC HDL TG	 180 ± 20.7 258.1 ± 20.5 45 ± 12.1 154 (median)	 150.4 ± 16.8 220.8 ± 20.9 37.0 ± 5.6 168.1 ± 64.1	 157.3 ± 41.8 (n=931) 246.1 ± 48.2 (n=1053) 47.0 ± 13.5 (n=1014) 225.4 ± 136.5 (n=1052)*

The EXCEL cohort included patients with higher baseline cholesterol levels than AFCAPS/TexCAPS and CUSTOM. Lipid values in CUSTOM were obtained on fasting or non-fasting samples whereas the controlled clinical studies required overnight fasting. Elevated mean TG levels in the CUSTOM cohort likely reflect this difference in biochemical testing. An analysis of baseline TG levels in the CUSTOM trial by fasting vs non-fasting sample does reveal a lower mean TG value for the fasting population (203.2 ± 126.4 mg/dL).

EXCEL
EXCEL was a randomized, double-blind, placebo-controlled study evaluating 5 treatment groups: lovastatin 20 mg q pm; lovastatin 40 mg q pm; lovastatin 20 mg bid; lovastatin 40 mg bid; and placebo. There were 1,642 patients randomized to the lovastatin 20 mg daily group. A 4- to 6- week diet-only, run-in, baseline period was followed by a 48-week diet and active treatment period. The primary efficacy endpoints were the proportion of patients achieving specific lipid goals at Week 48 of TC<200 and < 240 and LDL < 130 and 160. Mean percentage change from baseline at Week 48 was also calculated.

By Week 48, 31% of the lovastatin 20 mg daily treatment group had achieved an LDL-C < 130 mg/dL and the mean percent change from baseline was –24%. Mean changes for HDL-C and TG levels were +6.6% and –6.0%, respectively.

AFCAPS/TexCAPS
AFCAPS/TexCAPS randomized 6,605 patients to lovastatin 20 mg daily (n=3304) or placebo (n=3301). Lovastatin dose was titrated to 40 mg daily if at Week 18, LDL-C levels remained > 110 mg/dL. Approximately half of the lovastatin-treatment group were titrated to the 40 mg dose. The applicant presented data at Week 18 which represented only lipid-altering efficacy at the 20 mg daily dose. These data were available from only one of two sites which analyzed lipids during this clinical trial. Lipid-altering data at 1 year in only those patients remaining on the lovastatin 20 mg dose were also evaluated. The mean percent change in LDL-C from baseline in both analyses was approximately –24.0%. The applicant also presented the percent of patients reaching an LDL-C goal of < 130 mg/dL at Week 18. In these patients, 85.8% achieved and LDL-C goal of < 130 mg/dL.

<u>Reviewer Comments:</u>
Based on two large, placebo-controlled clinical trials evaluating lipid-altering efficacy of lovastatin, the expected mean reduction in LDL-C associated with the lovastatin 20 mg dose is 24%. The applicant has also summarized the proportion of patients in each of the two cohorts who achieved an LDL-C < 130 mg/dL while on lovastatin 20 mg. This analysis is intended to provide some estimate of the effectiveness of the nonprescription

product achieving NCEP-ATP III goals for the targeted OTC population. Only 31% of patients on lovastatin 20 mg in EXCEL achieved an LDL-C goal of < 130 mg/dL; however, this study enrolled patients with higher baseline cholesterol levels. As the mean LDL-C level was about 30 mg/dL higher in EXCEL compared to AFCAPS/TexCAPS and CUSTOM (see Table 3), it is not unexpected that a smaller percentage of this cohort would achieve the fixed target goal of < 130 mg/dL.

In contrast, the applicant summarized that by Week 18, 85.8% of the AFCAP/TexCAPS cohort who were OTC-eligible achieved an LDL-C goal of < 130 mg/dL. A similar analysis was performed by Week 6, a timepoint at which consumers are advised to get cholesterol testing if using OTC lovastatin. By Week 6, 86.2% of the AFCAPs/TexCAPS OTC-eligible population achieved an LDL-C goal of < 130 mg/dL with lovastatin 20 mg daily. It should be noted that during the conduct of AFCAP/TexCAPS, the two analytical labs performing lipid measures changed methods of analyses mid-study. Consequently, the proportion of OTC-eligible patients in AFCAPS/TexCAPS is summarized for only those patients with pre- and post-values using the same method (approximately two-thirds of the cohort).

In conclusion, in controlled clinical trials where patients enter dietary run-in periods, are selected by clinical investigators based on inclusion/exclusion criteria, and receive recommendations for dietary and lifestyle interventions, lovastatin 20 mg daily treatment results in mean reductions in LDL-C of 24%. Data from the AFCAPS/TexCAPS trial suggest that a significant proportion of patients who are OTC-eligible can achieve an LDL-C goal of < 130 mg/dL with lovastatin 20 mg. However, these data are based on an analysis after 6 and 18 weeks of therapy and data on long-term maintenance of this goal in a non-prescription setting are not available.

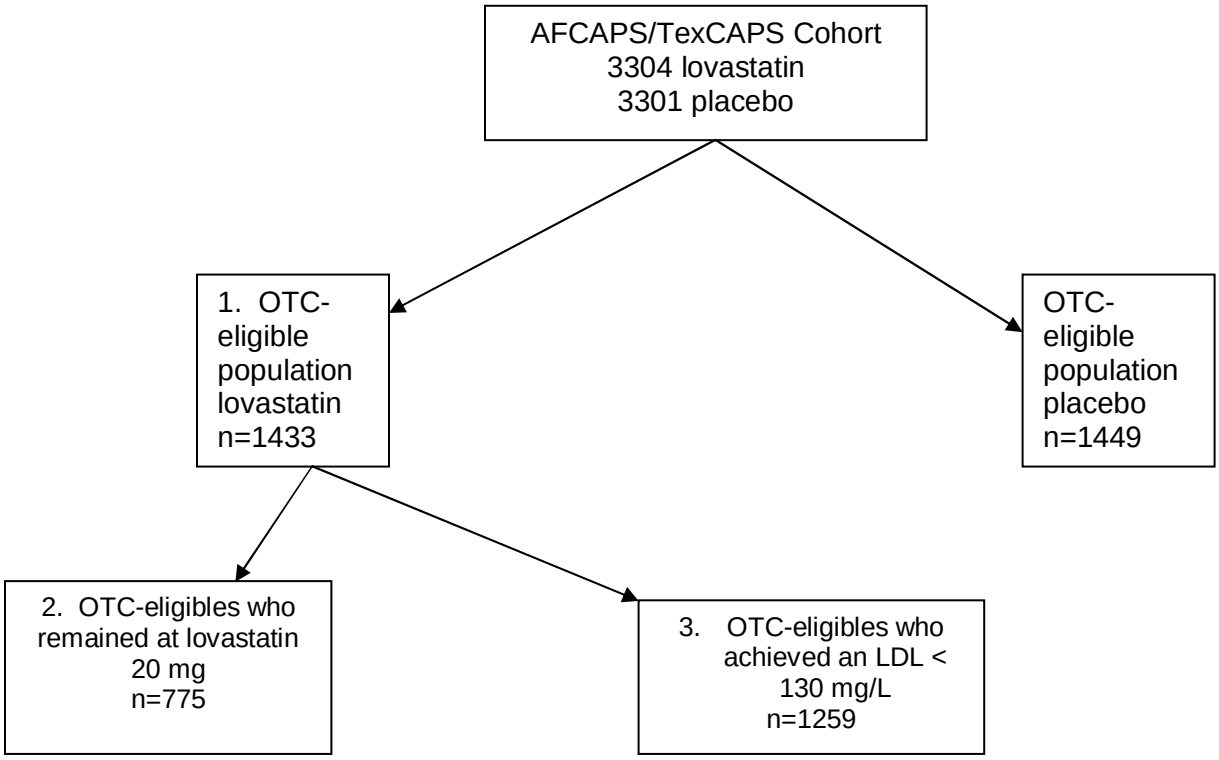
IV. B. Clinical Benefit

Elevated cholesterol level is an established risk factor for cardiovascular disease and its reduction has been shown in multiple clinical studies to reduce the risk of experiencing a CV event. Lovastatin is among several statins that have been proven to reduce CV event rates based on data from large, placebo-controlled clinical outcomes trials. For lovastatin specifically, that trial is AFCAPS/TexCAPS.

AFCAPS/TexCAPS was a 5-year, randomized, double-blind, placebo-controlled clinical outcomes study that evaluated the effects of lovastatin 20 to 40 mg daily on reducing the risk of one or more manifestations of atherosclerotic vascular disease. The primary endpoint of the study was a composite of unstable angina, fatal or non-fatal MI, or sudden death. Patients were randomized to placebo or lovastatin 20 mg and at Week 18, if LDL-C remained > 110 mg/dL, the lovastatin dose was increased to 40 mg with a randomly selected placebo patient matched for upward titration. Although a primary prevention study in individuals that might be considered at average risk for heart disease, this trial selected certain characteristics that marked relatively high short-term risk of heart disease. These characteristics included age (males ≥ 45 yrs and females ≥ 55 yrs) and a low HDL-C (males had to have HDL < 45 mg/dL and females < 47 mg/dL). Patients also had to have a Total-C/HDL ratio of > 6.0 if LDL-C was between 125 and 129 mg/dL. After an average follow-up period of 4.6 years, lovastatin 20 to 40 mg reduced the risk of experiencing a primary endpoint by 37% ($p<0.0001$) with 116 events (3.5%) occurring in the lovastatin group compared to 183 events (5.5%) in the placebo group.

A post-hoc analysis of the AFCAPS/TexCAPS database was undertaken by the applicant wherein three sub-populations were evaluated. These sub-populations can be described as follows:

Figure 1. Subpopulations evaluated in post-hoc analysis of clinical benefit



Subpopulation 1 was comprised of individuals in the AFCAPS/TexCAPS cohort who would have met the inclusion/exclusion criteria for Mevacor OTC use. Both the lovastatin and placebo groups were selected from the randomized cohort.

Subpopulations 2 and 3 are selected from Subpopulation 1. Subpopulation 2 would include only those patients from the lovastatin-treatment group who remained on 20 mg throughout the clinical trial. (i.e., those patients at Week 18 whose LDL-C were < 110 and did not require upward titration to 40 mg). Subpopulation 3 would include only those OTC-eligible patients from the lovastatin-treatment group who reached an LDL-C < 130 mg/dL at week 6.

Within each subgroup the applicant analyzed the observed event rate per 1000 patient-years at risk and the Kaplan-Meier event rates. For subpopulations 2 and 3, these event rates were also calculated for a matched control group. The following table derived from the applicant's submission summarizes these analyses and a calculated number needed to treat in each subpopulation.

Table 10.

Observed Versus Kaplan-Meier Event Rates for Each Subgroup by Treatment (AFCAPS/TexCAPS Study)

	N	No. of Events	Total Person Years of Follow-Up	Observed Event Rate (per 1000 Patient Years at Risk)	KM Event Rate (per patient over 6 years)	Number Needed to Treat‡
All AFCAPS/TexCAPS Participants						
Lovastatin	3304	116	17011	6.82	0.0383	34
Placebo	3301	184	16834	10.93	0.0678	
Mevacor® OTC-Eligible Participants						
Lovastatin	1433	48	7431	6.46	0.0347	25
Placebo	1449	88	7371	11.94	0.0748	
Non-Titrators						
Lovastatin	775	23	3960	5.81	0.0301	16
Placebo†	775	48	4018	11.95	0.0958	
To Reach OTC-Goal of LDL-C < 130 mg/dL at week 6						
Lovastatin	1259	42	6527	6.44	0.0354	28
Placebo†	1259	78	6431	12.13	0.0724	

† Refers to the matched set of placebo participants.
‡ The number needed to treat to avoid one CHD event was calculated using the Kaplan-Meier event rate estimated over a period of 6 years.

Based on this post-hoc analysis, the applicant concluded that the lovastatin treatment subpopulations had a significantly lower risk of having a CHD event than their placebo counterparts.

Reviewer Comments:
The comparisons between lovastatin treatment and placebo in subpopulations 2 and 3 do not represent comparisons of two randomized treatment groups. While baseline characteristics may appear similar based on matching criteria, randomized comparison ensures that imbalances that are expected and unexpected between treatment groups are eliminated. This cannot be assumed for subpopulations 2 and 3.

Subpopulation 2 (non-titrators) isolated those patients in AFCAPS/TexCAPS who maintained therapy with the proposed nonprescription dose of lovastatin 20 mg. However, this group of patients represents individuals in AFCAPS/TexCAPS who were able to achieve an LDL-C goal of < 110 mg/dL by Week 18 with lovastatin 20 mg. In the actual use study, proportion of consumers achieving an LDL-C goal < 110 mg/dL was not evaluated; however, the applicant did summarize the number of patients who purchased and used Mevacor OTC who achieved an LDL-C of < 100. From Table D-38 of sponsor's submission, only 208/1059 (19.6%) achieved this goal. It is unlikely that a nonprescription lovastatin 20 mg fixed dose will be able to achieve the LDL-C target therapy of AFCAPS/TexCAPS that was associated with the 37% risk reduction in the clinical trial.

Subpopulation 3 (OTC-eligible patients achieving LDL goal < 130 mg/dL by week 6) includes patients who subsequently had to have their lovastatin dose increased to 40 mg daily because an LDL-C goal of < 110 mg/dL (per AFCAPS protocol) was not achieved. The nonprescription program does not include recommendations for upward titration nor does it recommend a similar treatment goal.

While it is logical to assume that an individual taking nonprescription lovastatin 20 mg and has some reduction in cholesterol levels will also lower his/her risk of heart disease, a numerical assignment of risk reduction based on AFCAPS/TexCAPS is not possible. The estimates of risk reduction in the Mevacor-OTC eligible patient population are based on analyses of subpopulations in AFCAPS/TexCAPS that had an average treatment follow-up period of 5 years. During this follow-up period, dietary reinforcement and other risk factor modifications were provided to study participants. Study visits occurred every 6 weeks for the first 48 weeks of the study and every 6 months thereafter. The true risk reduction for nonprescription lovastatin use must factor in effectiveness of therapy (i.e., adequate LDL-lowering), long-term adherence to therapy and therapeutic lifestyle interventions, and appropriate management of other CHD risk factors. To date, the Agency only has 6 months of data for Mevacor 20 mg in the proposed OTC population.

In sum, even if one accepts the post-hoc subgroup analyses from AFCAPS, the NNT calculations represent truly a "best case scenario" assessment of the population effects, and thus of the probability of individual benefit, in CV risk reduction of Mevacor 20 mg OTC. While perhaps only 28 people meeting eligibility criteria and responding with the expected degree of LDL reduction would have to take lovastatin 20 mg daily for an average of approximately 5 years to save one event, it seems clear that the NNT would rise rapidly as the time-integrated lipid-altering effectiveness of the treatment regimen was reduced. At this time, however, we have no information on CV risk reduction with short-term or occasional treatment with lovastatin 20 mg, which would seem likely to characterize a significant proportion of Mevacor OTC use.

A separate memo from FDA statistician, Joy Mele, MS, on this analysis is included in this briefing document.

V. CLINICAL SAFETY

V. A. Muscle-Related Safety

Muscle toxicity with rare cases of rhabdomyolysis has been reported for all marketed statins. Clinical presentations are variable and can range from mild muscle aches and pains to severe muscle cell breakdown with renal failure that may be fatal. In clinical trials, patients have been identified with very elevated creatine kinase levels (e.g., > 10,000) in the absence of clinical symptoms. Myopathy, which is defined as CK elevations > 10x ULN with muscle symptoms, is estimated to occur between 0.1 to 0.6% of patients evaluated in clinical trials of statins across all doses studied. The more severe form of muscle toxicity, rhabdomyolysis, occurs less frequently and is estimated to have an incidence of 0.03 to 0.05%.[3]

The incidence of myopathy by dose in EXCEL was 0%, 0.1%, and 0.2% in the 20 mg daily, 40 mg daily, and 80 mg daily doses, respectively. No cases of rhabdomyolysis associated with lovastatin occurred in EXCEL while one patient treated with lovastatin 20 mg developed rhabdomyolysis in AFCAPS/TexCAPS. This case occurred in a patient who had recently undergone prostate cancer surgery. In this same study, 2 patients randomized to placebo had also developed rhabdomyolysis.

The applicant performed a search of its worldwide safety database of postmarketing adverse experience reports. Preferred terms of myopathy, muscle disorder NOS (not otherwise specified), myopathy toxic, myositis, myositis-like syndrome, polymyositis,

[3] Thompson PD et al. Statin-associated myopathy. *JAMA* 2003; 289(13):1681-1690.

rhabdomyolysis, myoglobin urine present, myoglobinuria, or blood myoglobin increased were selected. From approval (1987) until June 1, 2003, the applicant identified 874 reports containing one or more of the search terms. Based on an estimated worldwide exposure to lovastatin of approximately 27 million patient-treatment years, the applicant calculated a reporting rate of myopathy of approximately 3 per 100,000 patient years. Focusing only on reports of rhabdomyolysis, the applicant identified 334 reports representing a reporting rate of 1.2 per 100,000 patient-treatment years.

Evaluations of spontaneous adverse event reports for statin-associated muscle toxicity have also been performed by the FDA's Office of Drug Safety. From approval (1988) to July 2001, FDA reviewers retrieved 120 domestic cases of rhabdomyolysis in the Adverse Event Reporting System. Rhabdomyolysis was defined as CK > 10,000 IU/L with signs and symptoms and clinical diagnosis of rhabdomyolysis. Given the estimated numbers of prescriptions dispensed for lovastatin in the United States during this time period, the crude reporting rate of rhabdomyolysis per 100,000 prescriptions was 0.12.[4] A more recent analysis of the prescription claims database from 11 geographically dispersed U.S. health plans during January 1, 1998 through June 30, 2001 revealed too low usage of lovastatin to provide updated risk assessments for rhabdomyolysis.

Based on clinical trial data and different analyses of postmarketing spontaneous adverse event reports, the incidence of myopathy and rhabdomyolysis associated with lovastatin use is a very rare event. Given the lipid-lowering effects and clinical outcome data for lovastatin, the risk of myopathy/rhabdomyolysis does not appear to outweigh the benefit of lovasatin therapy.

The main concern of myopathy risk in the nonprescription setting is whether consumer behavior would differ from that in prescription use which would result in more individuals experiencing muscle toxicity than if they were receiving lipid-altering therapy as a prescription product. In this matter, two points require further discussion.

Firstly, the risk of muscle toxicity for lovastatin can be increased when the drug is co-administered with a potent CYP3A4 inhibitor with increase in exposure to lovastatin, a drug that will otherwise increase lovastatin drug levels, or a drug with inherent myotoxic effects. The following table summarizes the change in lovastatin exposure levels when it is co-administered with certain drugs/food that affect its bioavailability or metabolic clearance. These data are derived from pK studies performed by the applicant or published studies.

Table 11. Effect of coadministration of CYP3A4 inhibitors and gemfibrozil on Lovastatin Levels

	Number of Subjects	Dosing of Co-administered Drug or Grapefruit Juice	Dosing of Lovastatin	AUC Ratio[!] (with / without co-administered drug) No Effect = 1.00	
				Lovastatin	Lovastatin Acid
Erythromycin	12	500mg TID for 7 days	40mg QD for 7 days	5.7	N.A.
Gemfibrozil	11	600mg BID for 3 days	40mg (single dose)	0.96	2.8
Itraconazole	12	200mg QD for 4 days	40mg (single dose)	19	19
Grapefruit Juice (high dose)	10	200mL of double-strength[#]	80mg (single dose)	15	5

[4] Chang et al. Rhabdomyolysis with HMG-CoA reductase inhibitors and gemfibrozil combination therapy. *Pharmacoepidemiology and Drug Safety* 2004; 13:417-426.

[!]: results based on a chemical assay except one of results with grapefruit juice as indicated.
N.A.: not available
[#]: double-strength: one can of frozen concentrate diluted with one can of water. Grapefruit juice was administered TID for 2 days, and 200mL together with single dose lovastatin and 30 and 90minutes following single dose lovastatin on Day 3.

The applicant addresses this matter by including in the product label the recommendation that consumers ask their doctor or pharmacist before use if they are taking any prescription medicine or other cholesterol-lowering medicine, emphasizing that certain drugs can interact with lovastatin. The label also tells consumers to tell their doctor that they are taking nonprescription lovastatin before they start taking any new prescription medicine. As the list of interacting medications with lovastatin will increase over time (in the past 3 years verapamil, diltiazem, telithromycin, and danazol have been added to or are under negotiations for inclusion into the WARNINGS and PRECAUTIONS section of the label), the applicant is proposing that this labeling alerts consumers to consider every current and new drug as a potential interacting drug with lovastatin that would lead them to seek professional advice before taking or continuing lovastatin.

The second point for consideration is that the risk of muscle toxicity is increased with higher doses of statin. The dose proposed for nonprescription use has a modest effect on cholesterol-lowering compared to other approved statins, including those that are not CYP3A4 substrates. The potential of consumer upward titration of lovastatin to achieve recommended LDL-C treatment goals should be a consideration in evaluating the risks of muscle toxicity in the nonprescription setting.

V. B. Hepatic Safety

All statin labels were approved with recommendations for baseline and periodic post-baseline monitoring of hepatic transaminases. These recommendations arose from the observation that a slightly higher percentage of patients in controlled clinical trials developed transaminase elevations compared to placebo. However, these elevations rarely resulted in any serious clinical sequelae and rare postmarketing reports of hepatic failure are often complicated by other serious medical conditions and concomitant medical therapies such that attribution of event solely to lovastatin use is not possible.

The incidences of consecutive > 3x ULN increases in hepatic transaminases were evaluated in EXCEL and AFCAPS/TexCAPS. Both these studies excluded patients with baseline liver abnormalities. EXCEL excluded patients with any pre-existing elevation of liver transaminases while AFCAPS/TexCAPS excluded patients with hepatic transaminase elevations > 1.2 x ULN. The incidences of consecutive elevations >3x ULN in hepatic transaminases in both these studies are summarized in the following table:

Table 12. Frequency of Consecutive Liver Transaminase Elevations > 3x ULN in Clinical Trials

Consecutive > 3xULN elevations of ALT or AST	EXCEL					AFCAPS/TexCAPS	
	Lova 20 mg qd n=1642	Lova 40 mg qd n=1645	Lova 20 mg bid n=1646	Lova 40 mg bid n=1649	Pbo n=1663	Lova 20/40 mg n=3242	Pbo n=3248
	2 (0.1%)	12 (0.9%)	11 (0.9%)	20 (1.5%)	2 (0.1%)	18 (0.56%)	11 (0.34%)

Over the past 5+ years, several applications have been submitted to the FDA to reduce the recommendation for post-baseline monitoring of hepatic transaminases in different statin labels. Data from long-term, placebo-controlled studies strongly suggested that patients without clinical or laboratory evidence of liver disease could be safely treated with certain statins without monitoring of hepatic transaminase levels unless clinically indicated or if patients were treated with higher doses of the statin. Baseline monitoring is still recommended for all statins as no adequate data were available for patients with elevated hepatic transaminases or patients with chronic, asymptomatic liver disease (e.g., NASH or chronic hepatitis C). In short, while there seems little to no hepatic risk of statins in patients with normal hepatic function, the hepatic risks, if any, of statin therapy in patients with liver disease has not been studied. To the extent that much early liver disease is asymptomatic, this issue must be addressed in considering OTC availability of lovastatin.

The applicant had been informed in July 2002 that while data from controlled studies such as AFCAPS/TexCAPS and EXCEL might address the proposal to remove post-baseline monitoring of hepatic transaminase levels, these data would not remove recommendations for baseline testing as exclusion criteria of both these trials resulted in no safety data for those patients with chronic, asymptomatic liver disease who might be identified with a liver panel test.

In this resubmission the applicant references data submitted in a supplement to the prescription NDA that is currently under review. No new studies on the safety of lovastatin in patients with chronic liver disease were performed for this resubmission or the supplement to the prescription NDA. Testimonials from hepatologist consultants were recently submitted to the NDA to provide a rationale for not conducting prospective studies in patients with chronic, asymptomatic liver disease. The applicant has discussed in detail the findings from two studies submitted to both applications.

Study 1[5]
An abstract of a study conducted at the Weill Medical College of Cornell University was provided in this resubmission. The medical records of 14 patients who were started on a statin and whose liver profiles were available from baseline were reviewed. The liver profiles on 2 or more post-baseline assessments were also known in these subjects. These subjects comprised Group 1.

Retrospective data from 2 "control" groups were evaluated. Group 2 consisted of 14 patients with chronic hepatitis C who were on a statin and Group 3 consisted of 14 patients with hepatitis C virus who were not on a statin.

Lovastatin was not used by any subjects in the Groups 1-3. Statins used included atorvastatin, pravastatin, and simvastatin. The authors of this small study concluded the following:

- minor ALT and AST elevations are common in patients with chronic hepatitis C between 1 and 6 months after starting a statin and that none of the elevations resulted in changes in statin dose or discontinuation of medication

[5] Ahmed F and Jacobson IM. Safety of statins in patients with chronic hepatitis C (abstract)

- patients with chronic hepatitis C who are on a statin have slightly higher ALT and AST values than those who are not on a statin
- statins seem to be safe in patients with chronic hepatitis C but further studies on a larger number of patients are warranted

Study 2[6]
In another retrospective study conducted by investigators at the Indiana University School of Medicine, 3 cohorts were evaluated to determine the safety of statins in patients with elevated transaminase levels. Cohort 1 consisted of hyperlipidemia patients with elevated baseline liver enzymes who were prescribed a statin. Cohort 2 consisted of hyperlipidemic patients with normal baseline enzymes who were prescribed a statin. Cohort 3 consisted of patients with elevated liver enzymes who were not prescribed a statin but had follow-up ALT and/or AST. Patients with evidence of alcohol use, hepatitis B surface antigen, or hepatitis C antibody were excluded. Patients had to have had liver biochemistry results available from 6 months before and 6 months after starting a statin. Elevations in liver biochemistries were defined as mild to moderate or severe as follows:

- mild-to-moderate: elevations of AST and/or ALT *up to* 10 x ULN in patients with normal baseline enzymes or *up to* 10-fold elevations from their baseline values of AST and/or ALT in patients with elevated liver enzymes at baseline
- severe: the development of serum bilirubin > 3 mg/dL regardless of baseline transaminase values or elevations of AST and/or ALT *greater than* 10 x ULN in patients with normal baseline enzymes or *greater than* 10-fold elevations from their baseline values of AST and/or ALT in patients w/ elevate transaminase enzymes at baseline

The baseline mean AST and ALT values in the three cohorts are summarized in the following table.

Table 13. Mean Baseline Hepatic Transaminase Levels in Study Conducted by Chalasani et al.[6]

	Cohort 1 n=342	**Cohort 2 n=1437**	**Cohort 3 n=2245**
AST (IU/L)	55±37	22 ± 7	57 ± 49
ALT (IU/L)	43 ± 23	20 ± 8	61 ± 47

* the upper limits of normal for AST and ALT were 40 and 35 IU/L, respectively

The frequency of mild to moderate and severe transaminase elevations in the 3 cohorts is summarized in the following table:

[6] Chalasani N et al. Patients with elevated liver enzymes are not at higher risk for statin hepatoxicity. *Gastroenterol* 2004; 126:1287-92.

Table 14.

Frequency of Varying Degrees of Elevations in Liver Biochemistries Over a 6-Month Period in 3 Study Cohorts

	Cohort 1 (n=342)	Cohort 2 (n=1437)	Cohort 3 (n=2245)	p-Values	
				Cohort 1 vs. Cohort 2	Cohort 1 vs. Cohort 3
Mild/moderate elevations	4.7%	1.9%	6.4%	p=0.002	p=0.2
Severe elevations	0.6%	0.2%	0.4%	p=0.2	p=0.6

Cohort 1: Individuals with elevated baseline liver enzymes who were placed on a statin;
Cohort 2: Individuals with normal baseline liver enzymes who were placed on a statin;
Cohort 3: Individuals with elevated liver enzymes, but not placed on a statin.

Patients with baseline elevated hepatic transaminase elevations had significantly higher rate of mild to moderate elevations with statin therapy compared to patients who had normal baseline values treated with statins. (Cohort 1 vs. Cohort 2). However, there were no differences in enzyme elevations between Cohort 1 and patients who had baseline enzyme elevations who were not treated with statins (Cohort 3). The authors stated that this finding might suggest that mild-to-moderate elevations in transaminase elevations may be independent of statin exposure and reflect more the natural course of the medical condition resulting in baseline transaminase elevations. While this may be a logical conclusion, patients with certain known liver conditions were excluded from this study.

These authors also compared Cohort 1 to an additional control group consisting of 1,111 individuals with detectable hepatitis C antibody (not treated with statins or interferon) who had elevated baseline AST or ALT. Compared with Cohort 1, individuals with hepatitis C had a significantly higher frequency of mild-to-moderate or severe elevations in liver biochemistries. This comparison provided no safety data for *statin use in patients with chronic hepatitis C*.

The applicant reviewed the worldwide adverse experience safety database for selected hepatobiliary adverse experience. As of June 1, 2003, there were 25 cases of hepatic failure/hepatic necrosis and 251 reports of “hepatitis” reported for lovastatin. Given an estimated worldwide exposure to lovastatin of approximately 27 million patient-years, the calculated reporting rate of hepatic failure/hepatic necrosis and “hepatitis” is 1.0 and 10.4 reports, respectively, per million patient-years of treatment.

Similarly, the FDA’s Office of Drug Safety searched AERS for domestic reports of liver failure associated with statin use. Three preferred terms were used in the search criteria: liver failure, hepatic encephalopathy, and liver transplant. A consult was conducted in March 2001 and updated recently in November 2004. As of February 25, 2000, there were 14 domestic reports of liver failure associated with lovastatin use. As of November 5, 2004, there were 20 reports. Reporting rates were calculated for the 4-year period post-approval in the March 2001 consult. As summarized by the FDA epidemiologist, the reporting rate for lovastatin was estimated at 2 cases per million person-years of exposure which approximates the background rate of idiopathic liver failure of approximately 1 per 1,000,000 person-years.

In conclusion, transaminase elevations occur with statin therapy; however, large databases from clinical trials and postmarketing use suggest that these increases rarely result in serious liver injury and in the few reports of liver injury, attribution to statin use cannot be established. While such data would strongly support the recommendation that post-baseline monitoring be obtained only when clinically indicated, the Agency has conveyed to the applicant that information is needed to determine if baseline monitoring is still required to identify those patients with asymptomatic liver disease. These chronic liver diseases would include nonalcoholic fatty liver disease (NAFLD), hepatitis C, hepatitis B, and alcoholic liver disease in which the patient may be unaware of their condition. It has been estimated that NAFLD affects 10 to 24% of the general population and that 1.8% of the U.S. population is positive for hepatitis C antibodies.[7,8] In a supplement submitted to the prescription NDA for lovastatin, the applicant is proposing the WARNINGS section of the label include the following modification:

"*It is recommended that liver function tests be performed prior to initiation of therapy in patients with a history of liver disease, or when otherwise clinically indicated. It is recommended that liver function tests be performed in all patients prior to use of 40 mg or more daily and thereafter when clinically indicated*. "

This supplement is still under review; however, it should be noted that the proposed language will not remove baseline monitoring for lovastatin. The proposed label recommends that the prescriber consider a patient's history of/for liver disease and obtain the laboratory tests prior to initiating drug therapy. In the nonprescription setting, this recommendation would also require the applicant to demonstrate that consumers can identify whether they have a history of liver disease, risk factors for liver disease, or clinical signs and symptoms suggestive of liver disease to decide if they should obtain baseline LFTs prior to purchasing and using the product.

VI. COMMENTS ON NONPRESCRIPTION MEVACOR 20 MG PROGRAM

The October 2000 non-approval letter to the applicant stated that "*neither the rationale for treating the proposed target population with Mevacor 10 mg in the over-the-counter (OTC) setting, nor a favorable benefit/risk ratio for such treatment has been adequately established. Furthermore, the ability of consumers to appropriately self-select and to adequately comply with chronic Mevacor therapy without the intervention of a physician has not been demonstrated".*

In this resubmission to NDA 21-213, the applicant has selected a patient population that has "*≥2 risk factors for CHD and a ≤20% risk of CHD over 10 years without underlying chronic conditions that complicate consumer self-management*". Based on NCEP ATP-III guidelines, these are individuals in which lipid-altering drug therapy should be considered if, after therapeutic lifestyle changes, LDL-C remains ≥ 130 (or ≥ 160 if 10-year risk for CVD is < 10%). The treatment goal for these individuals is an LDL-C goal of < 130 mg/dL. The applicant has proposed that a daily fixed dose of lovastatin 20 mg will effectively treat this population with respect to meeting LDL-C goals and CHD risk reductions.

[7] Angulo, P. Nonalcoholic fatty liver disease. *NEJM*. 346(16): 1221-1231.

[8] Lauer, GM and Walker BD. Hepatitis C virus infection. *NEJM.* 345(1):41-52.

Data from controlled clinical trials, in particular, AFCAPS/TexCAPS, suggest that lovastatin 20 mg daily will allow a majority of OTC-eligible patients to achieve an LDL-C goal of < 130 mg/dL. Based on a post-hoc analysis of a subgroup of AFCAPS/TexCAPS patients and a non-randomized comparison, the sponsor proposes that among approximately 28 individuals achieving such an LDL-lowering effect and complying with the daily treatment regimen for up to 6 years, data from AFCAPS suggest that one atherosclerotic event will be prevented. The extent of population benefit and of individual risk reduction with lesser degrees of compliance and shorter terms of treatment is not known.

Data from controlled clinical trials and post-marketing spontaneous adverse event reporting support the conclusion that risks of muscle and hepatic toxicity are rare events that do not offset the benefits associated with long–term use of lovastatin 20 mg in otherwise healthy individuals. The hepatic risks of lovastatin 20 mg daily in patients with baseline liver disease of certain etiologies have been addressed in the amended application, though no prospective investigations in patients with diverse forms of asymptomatic liver disease have been conducted. The extent to which the data presented can be extrapolated to the types of liver disease generally prevalent in the OTC target population must be considered. Other safety concerns include drug-drug interactions which affect the risk of myopathy and exposure during pregnancy. The sponsor proposes to manage these risks through labeling.

The Rx-to-OTC switch of Mevacor 20 mg must not engender novel or augmented risks nor significantly undermine effectiveness of the drug in the prevention of cardiovascular disease. For optimally safe use, the consumer must appropriately self-select as eligible for therapy after excluding factors that would increase the risk of drug side effects (e.g., pregnancy, liver disease) and elect discontinuation of therapy when situations arise that would alter the risk of therapy (e.g., newly prescribed interacting drug, development of myopathy). For optimal efficacy and avoidance of undertreatment, the consumer must appropriately self-select based on LDL level and CVD risk factor profile, must seek follow up and take appropriate action based on response (e.g., discontinue and seek physician intervention if response is inadequate). Additionally, the consumer should understand that management of hypercholesterolemia is chronic. Adherence to medications and compliance to diet and life-style modifications are essential components of this management. Consumers must also understand that their individual risks for heart disease may change over time based on age, development of heart disease, or other factors (e.g., elevated blood pressure, development of diabetes). With these changes, consumers must understand that target therapies may be lower and that they may have to seek appropriate management to achieve these new goals. Finally, the field of lipid biology, atherosclerosis, and CV risk management will evolve over time as new data emerge. A nonprescription program that will be affected by changing treatment guidelines must be adaptable to these and other changes in the state of the relevant basic and clinical science in order to ensure appropriate consumer behavior and ongoing safety and efficacy of the OTC treatment regimen.

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/s/

Mary Parks
1/19/05 12:51:54 PM
MEDICAL OFFICER

David Orloff
1/19/05 04:06:12 PM
MEDICAL OFFICER

MEMORANDUM OF CONSULTATION

Date: December 9, 2004 (draft) January 25, 2005 (DFS version)
Between: Mary Parks, M.D., Clinical Team Leader (HFD-510)
and
Joy D. Mele, M.S., Statistical Reviewer (HFD-715)
Subject: Mevacor OTC NDA 21213

This memorandum addresses Section 1.6.1.2.5 entitled "Defining the Benefit of Lovastatin 20 mg once daily in the Mevacor OTC Eligible Population".

The applicant (Merck Research Laboratories) performed analyses of the AFCAPS/TEXCAPS data to estimate the possible effect of 20 mg (the proposed OTC dose) of lovastatin on clinical endpoints in an OTC eligible population. The selection criteria for AFCAPS/TEXCAPS and the OTC-eligible population are summarized in Table 1.

Table 1. Selection criteria for Study AFCAPS/TEXCAPS and the proposed OTC-eligible population

	AFCAPS/TEXCAPS	OTC-eligible
Age	Male≥45; Female≥55	Male≥45; Female≥55
LDL-C	125-129 if TC/HDL>6 130-190	130-170
Risk factors HDL smoker family history high BP	Must have low HDL Male ≤45; Female≤55 yes yes controlled BP only	At least one risk factor <40 yes yes yes
Evidence of CVD	Excluded	Excluded

The primary difference between the criteria is that AFCAPS/TEXCAPS patients all had "low" HDL while the OTC patients must have at least one risk factor which may or may not include low HDL.

Reviewer's Comments:
The results of AFCAPS/TEXCAPS may not be applicable to patients who do not have low HDL; however, evidence from the Heart Protection Study suggests that similar patients without evidence of cardiovascular disease who have high HDL and a risk factor for CHD (such as diabetes, hypertension or peripheral/cerebral vascular disease) receive beneficial effects from statin therapy.

The applicant looked at three subgroups of patients from AFCAPS/TEXCAPS; 1) patients meeting the OTC eligible criteria at baseline, 2) patients who reached goal without titrating up to 40 mg and 3) patients who achieved an LDL of less than 130 on treatment (these groups are described in more detail in Dr. Parks' review).

Reviewer's Comments:
Patients in Groups 2 and 3 were selected based on their response and so those groups do not represent proper subgroups (i.e. randomized groups); therefore, the results of Groups 2 and 3 are not reviewed here. The drawback to Group 1 is that about ½ the patients were titrated to the 40 mg dose. In fact the applicant stated that because of the titration, "direct estimation of the benefit of 20 mg … is not possible" (page D-61 of the NDA).

The results for the OTC eligible subgroup and the complete AFCAPS/TEXCAPS population from the NDA under review (2004) and from a previous submission dated December 10, 1999 are summarized in the table below. Note that the definition of OTC eligible differed between the submissions; in the previous submission, men had to be 40 or older, patients with a history of high blood pressure were excluded and there was no criteria for HDL.

Table 2. AFCAPS/TEXCAPS Event rates and Number-Needed-to-Treat (NNT) as reported by the applicant in NDA's submitted in 1999 and 2004

	Placebo	Lovastatin	NNT
1999 NDA			
All Pts			
Events	183/3301	116/3304	
5 YR K-M rate	5.2%	3.3%	54
OTC- Eligible			
Events	108/1921	60/1884	
5 YR K-M rate	5.3%	3.0%	43
2004 NDA			
All Pts			
Events	184/3301	116/3304	
6 YR K-M rate	6.8%	3.8%	34
OTC- Eligible			
Events	88/1449	48/1433	
6 YR K-M rate	7.5%	3.5%	25
FDA review of AFCAPS/TEXCAPS All Pts.			
Events End of Study	183/3301	116/3304	
K-M Rate	7.2%	5.1%	48

Event=cardiac death, fatal or non-fatal MI or unstable angina

Reviewer's Comments:
The difference between the rates and the NNT in the above table is due to the length of observation periods; the 1999 rates were based on 5 year estimates while 2004 rates are based on 6-year estimates. The last row shows the Kaplan-Meier estimates presented in the FDA review of AFCAPS/TEXCAPS which is much closer to the 5-year treatment effect. It is worth noting that there were only two centers in AFCAPS/TEXCAPS and one center (with 43% of the patients) had a maximum follow-up of 5.1 years. A small number of patients completed 6 years of treatment. This reviewer concludes that the NNT estimates presented in the submission under review (the 2004 submission) are not acceptable and underestimate the NNT.

The statistician on the DMEDP/OTC advisory committee (Dr. Dean Follman) requested information regarding the five and six year NNT values. The following information was provided by the applicant.

Merck's explanation of 5-year and 6-year computations of event rates:

Calculations Based on the Kaplan-Meier Event Rates

Tables D-34a and D-34b summarize the calculations based on the Kaplan Meier survival method over 5 and 6 years for all individuals in AFCAPS/TexCAPS and for only those individuals enrolled in AFCAPS/TexCAPS who are

label-eligible. The first column of these tables give the estimated CHD event rates for the placebo and lovastatin groups, as well as the standard errors for these values. The absolute risk reduction (ARR) is then calculated as the difference in the Kaplan-Meier event rates between the treatment groups. The number needed to treat is given in column 4 and is the reciprocal of the absolute risk reduction. To calculate the 95% confidence interval for the number needed to treat, I used the method described by Altman, et. al. (BMJ, 1999; 319:1492-1495). The lower and upper bounds of the 95% confidence interval for the number needed to treat are the reciprocals of the upper and lower bounds of the ARR. The standard error for the absolute risk reduction was calculated using the following formula:

$$SE(ARR) = \sqrt{\{[SE(Lovastatin)]^2 + [SE(Placebo)]^2\}}.$$

The 95% confidence interval for the ARR was then found using the following formula:

$$ARR \pm 1.96 * SE(ARR).$$

It is evident from Tables D-34a and D-34b that participants in the lovastatin treatment group tend to have lower event rates than their counterparts in the placebo group.

Table D-34a
Kaplan-Meier Event Rates for Each Subgroup
By Treatment
Over 5 Years

	KM Event Rate (standard error)	Absolute Risk Reduction (standard error)	95% Confidence Interval for the Absolute Risk Reduction	Number Needed to Treat[1]	95% Confidence Interval for the Number Needed to Treat
All AFCAPS/TexCAPS					
Lovastatin	0.03253 (0.00316)	0.01904 (0.0051)	(0.0091, 0.0289)	53	(35, 110)
Placebo	0.05157 (0.00394)				
Mevacor™ OTC label-eligible Participants					
Lovastatin	0.03129 (0.00474)	0.0235 (0.0077)	(0.0084, 0.0386)	43	(26, 120)
Placebo	0.05476 (0.00608)				

Table 34b
Kaplan-Meier Event Rates for Each Subgroup
By Treatment
Over 6 Years

	KM Event Rate (standard error)	Absolute Risk Reduction (standard error)	95% Confidence Interval for the Absolute Risk Reduction	Number Needed to Treat[1]	95% Confidence Interval for the Number Needed to Treat
All AFCAPS/TexCAPS					
Lovastatin	0.0383 (0.00376)	0.0295 (0.0067)	(0.0163, 0.0427)	34	(24, 62)
Placebo	0.0678 (0.00556)				
Mevacor™ OTC label-eligible Participants					
Lovastatin	0.0347 (0.00532)	0.0401 (0.0103)	(0.0199, 0.0603)	25	(17, 51)
Placebo	0.0748 (0.00882)				

Reviewer's Comments:

The above information provided by Merck clearly shows the unstableness of the NNT with large differences between the 5 year and 6 year calculations. About half of the OTC eligible population completed 5 years on study and about 1/5 completed 6 years on study.

Overall this reviewer thinks that there is a body of evidence from several statin trials that suggest that a wide range of patients may receive clinical benefit from statin therapy; however, none of the clinical endpoint trials were conducted in a population limited to Merck's targeted OTC population and treated with only 20 mg of Mevacor. Also as mentioned by FDA reviewer David Hoberman in a statistical review of the 1999 NDA, a critical factor to consider is that "the compliance in AFCAPS/TEXCAPS is probably much greater than that in a true OTC setting." Estimates from a closely monitored population may not represent what we could expect in an OTC population.

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/s/

Joy Mele
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Todd Sahlroot
1/26/05 04:12:31 PM
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PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA 21-213
Review number: 2
Sequence number/date/type of submission: 000, complete response to NA letter, 10/24/04
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Merck
Manufacturer for drug substance: Merck

Reviewer name: Karen Davis-Bruno; Ph.D.
Division name: DMEDP
HFD #: 510
Review completion date: 1/27/05

Drug:

Trade name: Mevacor Daily
Generic name (list alphabetically): nonprescription lovastatin
Code name:MK-0803, L-154803
Chemical name: see NDA 19-643
CAS registry number: see NDA 19-643
Mole file number: see NDA 19-643
Molecular formula/molecular weight: see NDA 19-643
Structure: see NDA 19-643

Relevant INDs/NDAs/DMFs: NDA 19-643, NDA 19-643/S061

Drug class: HMG CoA reductase inhibitor (statin)

Indication: an adjunct to diet and exercise in individuals with LDL 130-170 mg/dl and multiple risk factors for CHD in men ≥45 years and postmenopausal women ≥55 years old.

Clinical formulation: see NDA 19-643; 20 mg/day is the proposed OTC dose for Mevacor Daily

Route of administration: oral

Proposed use: see Indication

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Executive Summary

I. Recommendations

A. Recommendation on Approvability: Extensive nonclinical reproductive/developmental toxicity data suggest a potential to induce fetal/neonatal mortality, structural/behavioral/learning developmental and skeletal malformations at exposures in animals similar to those expected following a 20 mg/day clinical dose. Mevacor OTC is proposed for use in post-menopausal women ≥55 yrs. However based on the sponsor's actual use trial data and label comprehension study it appears that women <55 yrs. may have inappropriately self-selected Mevacor Daily (20 mg/day OTC). Pharmacology/Toxicology suggests that this potential risk needs to be adequately addressed by the sponsor perhaps through labeling and education/training of the proposed marketed population and defers to the clinical review team to determine the most appropriate way to address the potential risk in this population.

B. Recommendation for Nonclinical Studies: N/A

C. Recommendations on Labeling: Pharmacology/Toxicology suggests that the potential developmental risk identified in nonclinical studies needs to be adequately addressed by the sponsor perhaps through labeling and education/training of the proposed marketed population.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings: refer to NDA 19-643

B. Pharmacologic Activity: HMG CoA reductase inhibition

C. Nonclinical Safety Issues Relevant to Clinical Use: The potential for inappropriate self-selection of this product in an OTC setting based on the actual use trial and label comprehension study submitted, accentuates a safety issue regarding in advertent fetal exposure to Mevacor during the first trimester of pregnancy in women. The weight of evidence from two decades of animal reproductive/developmental toxicity studies demonstrates that Mevacor has the potential to induce fetal/neonatal mortality, decreased body weight, behavioral/learning delays and skeletal malformations in the fetus/neonate irrespective of the presence of maternal toxicity.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____

(see memo attached)

C. cc: list:

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PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY: SEE NDA 19-643

II. SAFETY PHARMACOLOGY: SEE NDA 19-643

III. PHARMACOKINETICS/TOXICOKINETICS: SEE NDA 19-643

IV. GENERAL TOXICOLOGY: SEE NDA 19-643

V. GENETIC TOXICOLOGY: SEE NDA 19-643

VI. CARCINOGENICITY: SEE NDA 19-643

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY: SEE NDA 19-643 ORIGINAL & S#061 REVIEWS

VIII. SPECIAL TOXICOLOGY STUDIES: SEE NDA 19-643/S061

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Merck is proposing to market Mevacor (lovastatin) 20 mg/day in an OTC setting as an adjunct to diet and exercise in individuals with LDL 130-170 mg/dl and multiple risk factors for CHD. Mevacor OTC is proposed for men ≥45 years and post-menopausal women ≥55 years. Mevacor was the first approved HMG-CoA reductase inhibitor (statin) and has been marketed as a prescription-only drug since 1987 to lower cholesterol. The potential for inappropriate self-selection of this product in an OTC setting, however accentuates a safety issue regarding in advertent fetal exposure to Mevacor during the first trimester of pregnancy in women. The weight of evidence from two decades of animal reproductive/developmental toxicity studies demonstrates that Mevacor has the potential to induce skeletal malformations and developmental delays in the fetus/neonate irrespective of the presence of maternal toxicity.

HMG-CoA reductase is the rate limiting enzyme in de novo cholesterol biosynthesis which converts hydroxymethylglutaryl-CoA to mevalonic acid. Lovastatin is a lactone pro-drug that is converted to the active open acid form by plasma and tissue esterases. Merck proposes that fetal skeletal malformations observed in rats given high doses of Mevacor (≥400 mg/kg/day) are secondary to maternal toxicity produced early in gestation and that this toxicity is pharmacologically based. Therefore studies with co-administered mevalonate; the metabolic product of HMG-CoA reductase were performed to eliminate the maternal toxicity and hence prevent the fetal skeletal malformations observed with Mevacor. Additional studies using subcutaneous instead or oral administration of Mevacor prevented the maternal toxicity (forestomach acanthosis, hyperkeratosis) and prevented the skeletal anomalies according to the sponsor. Merck proposes that the any developmental delays observed in post-natal rats occur at significant clinical exposures and therefore is not a clinical concern. However this conclusion is based on a limited post-natal neurodevelopmental assessment following direct dosing of neonatal rats which inadequately addressed the original concern for post-natal neurodevelopmental abnormalities because of the study's limited scope.

The original nonclinical safety assessment of lovastatin included developmental toxicity studies (fertility, embryo-fetal, and pre- and postnatal development) in rat and rabbit with lovastatin and its active metabolite (open acid form). Additional developmental studies were performed following market approval in 1987 through 1999. In 1999 Merck submitted NDA 21-213 for a 10 mg nonprescription form of lovastatin for the treatment of elevated cholesterol for primary prevention of coronary heart disease. A pharmacology/toxicology safety concern arose from review of this application involving the potential fetal risk of lovastatin use by women (of child-bearing potential) in an OTC setting. Prescription Mevacor is labeled as Pregnancy Category X as are all of the statins based on the established effects on cholesterol synthesis of this drug class. The Pregnancy Category X designation is equivalent to a contraindication for use of a product during pregnancy based on studies in animals or experience in humans demonstrating adverse fetal effects whereby the fetal risk outweighs the benefit to the mother. The battery of reproductive toxicity studies conducted for lovastatin using standard study designs inadequately assess potential drug effects on neuronal developmental processes that occur post-natally in the rat (e.g. myelinization) and during the second and third trimester in humans. This contention was supported by the CDER PTCC Reprotoxicity Committee and members of the Pharmacology/ Toxicology Senior Leadership Team. Both groups recommended additional postnatal neurodevelopmental studies to address this data gap and clinical concern.

A neurodevelopmental toxicity study using direct dosing of neonatal rats was recommended to include evaluations of exposure, establishment of a NOEL (no observed effect level), detailed brain histology and behavioral/developmental/functional assessments. Merck submitted a dose range finding study and definitive study protocols on 5/22/01. The Division and the CDER PTCC Reprotox Committee provided detailed feedback on the protocol design in advice letters of 7/01, 5/02, 11/02 and 10/03. The final study reports were submitted for review 4/04.

Nonclinical Safety Issue Relevant to Clinical Use: Inadvertent first trimester fetal exposure to lovastatin prior to a woman realizing she is pregnant in an OTC setting is a concern. It is likely that potential fetal risk in females of reproductive potential is manageable in the prescription setting under the guidance of a physician. It becomes less clear under an OTC setting for this population particularly with inappropriate self-selection. Clinical data obtained during pregnancy is very limited, but does exist. The numbers of cases are too few to demonstrate any correlation; however the pregnancy outcomes do not allay the concern for inappropriate self-selection. An April 8, 2004 letter to NEJM examining adverse event reports (AEs) in the FDA AERS database from 1987-2001 finds 5 cases associated with CNS and limb deficiency anomalies from 52 cases of lovastatin exposure during pregnancy. These abnormalities are exceedingly rare in the general population. In 2/5 of these cases pregnant women were exposed to doses at or below the proposed OTC dose of 20 mg/day.

The Office of Drug Safety (ODS) was consulted to update the pregnancy outcome data from the FDA AERS database of *in utero* exposure to statins; 25/195 cases were reported for lovastatin. These 25 cases involved 9 elective terminations, 4 spontaneous terminations, 1 unknown outcome and 11 live births. Among the live births 6 cases had normal outcomes, 4 had birth defects and 1 had other complications as outlined in the following table. Data was available on one of the elective terminations.

Live Births with Defects	Findings	Lovastatin Dose	Prenatal Exposure
Case 1	Malformations: musculoskeletal-upper extremity, dentofacial & breast, dysmorphic features-ptosis, torticollis, hemangioma, joint disorder	unknown	~2 weeks
Case 2	Left hand tag, non-functional thumb, holoprosencephaly, hydrocephalus	40 mg	~6 weeks
Case 3	Aortic hypoplasia, atrial & ventricular septal defect, 2^0 cerebral dysfunction, mortality day 2	40 mg	~5 weeks
Case 4	Right auditory canal absent [concomittent meds: ethinyl estradiol/ethynodial diacetate, pseudoephedrine, acetaminophen]	unknown	~8 weeks
Case 5	5 year old: attention deficit disorder, seizures, ataxia, abnormal fine motor movement	unknown	~ 8 weeks
Data on elective terminations			
Case 1	Spina bifida, hydrocephalus	20 mg	3 -18 weeks

The most common birth defects in the US are cardiac and circulatory at 260.4/100,000 live births followed by musculo-skeletal and connective tissue defects at 239.4/100,000 live births (or ~0.2%) according to the National Vital Statistics System [http://www.cdc.gov/nchs/data/nvsr/nvsr49/nvsr49_01.pdf]. The number of reported exposures is small and the true rate of occurrence for the reported defects is unknown because these reported cases were spontaneous reports to the AERS database. A causal association between *in utero* statin exposure and identified birth defects cannot be made based on the current information. ODS suggests that latent effects such as birth defects are best captured through a registry system which is not available for statins.

Nonclinical studies: Animal reproductive toxicity studies are designed to address the potential for adverse developmental (*in utero*) risk. Standard reproductive study designs focus on *in utero* exposure before/during conception (Segment I), organogenesis (Segment II) and through lactation (Segment III). These studies are designed to assess acute toxic effects with some sensitivity. However they are not designed to evaluate subtle or long-term effects.

Skeletal/Developmental Abnormalities: Merck contends that reproductive studies performed 1980-1999 revealed skeletal anomalies in rats at maternally toxic doses (≥400 mg/kg/day). The observed fetal skeletal abnormalities are likely attributable to fetal nutritional deficits due to reductions in maternal food intake and body weight secondary to maternal acute forestomach edema/inflammation leading to acanthosis/hyperkeratosis with repeated oral dosing. The forestomach is an organ specific to the rat and therefore this toxicity is not relevant to humans. Although the cellular mechanism is unknown, Merck suggests that marked upregulation of the forestomach modified squamous epithelium HMG-CoA reductase is possible. This has been demonstrated in rodent hepatocytes following lovastatin treatment (PNAS 85:5264-5268, 1988; Fd Chem Toxic 29(9):621-628, 1991). Merck contends that the HMG CoA reductase up

regulation resulting in forestomach histopathology in the rat is reversible with mevalonate co-administration substantiating the pharmacologic basis of the lovastatin induced effect on the rodent forestomach. However, maternal mortality during gestation is observed with co-administration of mevalonate. It appears that the mortality is a result of esophageal erosion/perforation which is usually indicative of a gavage error; however, it is only the mevalonate treated dose groups that have this finding which is reproduced in two separate studies. There are fetal skeletal findings in the mevalonic acid co-administered groups consistent with the other reprotoxicity studies with lovastatin alone. Merck's basis for establishing that fetal skeletal anomalies are the result of maternal toxicity follows: 1) Elimination of maternal toxicity by alternate dosing regimens (e.g. SC to avoid forestomach toxicity seen with oral administration) eliminates all fetal skeletal abnormalities despite maintaining comparable or greater maternal and fetal drug exposure levels; 2) The dose response for fetal skeletal abnormalities is identical to that for incidence and severity of maternal toxicity. This is consistent with a literature report that dietary nutrient deficiencies in rats can produce vertebral, rib and sternebral malformations; 3) Maternal, embryonic, and fetal exposures to lovastatin during the critical period for osteogenesis (GD 15) do not correlate with the presence of skeletal abnormalities; 4) Suppression of fetal mevalonate concentration does not correlate with the presence of skeletal abnormalities.

Based on the animal data reviewed over the past 20 years (1980-1999) fetal toxicity including mortality, body weight decrements, skeletal malformation and behavioral/learning delays in the absence of maternal toxicity was observed at drug exposures comparable to the low therapeutic dose range (10-20 mg/day).

The Division's interpretation of the reproductive toxicity findings with Mevacor differ from Merck.

Selected Lovastatin Reprotoxicity Studies	Route	Doses (m/k/d)	Maternal NOAEL (m/k/d)	Exposure Multiple *	Rat Fetal/Neonate Findings+				
					Death	Skeletal Malformations	Develop-mental Delays	Decrease Weight	External/ Visceral Malformations
Segment I (Dosing 15 Days prior to mating through Gestation Day 20)									
1. 80-709-0	Oral	8,80,800	80 8	60X 6X	√	√	√	√	√
2. 85-708-0	Oral	2,20,200	20 2	15X 2X	√			√	
3. 85-728-0-1	Oral	15,240	15	5X	√			√	√
Segment II (Dosing Gestation Day 6-20)									
4. 80-714-0	Oral	8,80,800	80	60X		√			
5. 98-739-0	SC Oral	12.5,25 400	≤25	<1X	√	√ @12.5 incomplete ossification	√	√	
6. 96-728-0	Oral	100,200,400,800	100	75X		√		√	
7. 97-728-0	Oral	100,200,400,800	100	75X		incomplete ossification		√	
Segment III (Dosing Gestation Day 15-Lactation Day 21)									
8. 85-707-0-1	Oral	2,20,200	20	15X	√		√		

* OTC therapeutic dose=20 mg/day=$AUC_{0\text{-}24h}$=30±15 ng h/ml ; + No maternal toxicity defined as >10% decrease in body weight gain or forestomach toxicity.

At ≤5 X therapeutic exposure following a 20 mg/day lovastatin dose, fetal mortality, and decreased body weight is observed. At therapeutic exposures ≥6X a 20 mg/day OTC dose neonatal developmental delays are observed in free-fall righting reflex, negative geotaxis, auditory startle response, swimming and reduced latency in the open field test, incomplete skeletal ossification is seen. At higher exposures of >25X therapeutic exposure, skeletal malformations are observed consisting of increased supernumerary ribs, incomplete bone ossification, wavy ribs. Animal studies have indicated that Mevacor (lactone) crosses the placenta and is secreted in milk compared to plasma (1:1.5). The cholesterol source in rat embryos is obtained from the yolk sac or placenta (maternal source); de novo synthesis contributes a minor portion of fetal cholesterol. Since lovastatin and other hydrophobic HMG CoA reductase inhibitors can enter fetal circulation there is still a clinical concern for fetal findings following exposure during organogenesis. A rat maternal NOAEL=80 mg/kg/day (AUC=1900 ng h/ml on GD 20) is suggested based on the data presented. Fetal/F1 pup mortality, decreased weight gain, skeletal findings (wavy ribs) and incomplete ossification are observed reproducibly in prior reprotoxicity studies in litters exposed to 2-80 mg/kg/day, but are unexplained. Developmental/behavioral effects showed a similar pattern. This would suggest a

rat developmental NOAEL<2 mg/kg/day (less than clinical exposure at 20 mg/day based on body surface area).

The majority of studies were performed in rat however similar effects were seen in a limited number of studies in rabbits and mice. Rabbits show a developmental NOAEL at ≤ 5 mg/kg/day (or 60 mg/m^2 providing a 5X safety margin to the therapeutic dose of 20 mg/day=12 mg/m^2). In rabbit visceral abnormalities are seen at 15 mg/kg/day (15X exposure following a 20 mg/day clinical dose) with higher doses of 25 mg/kg/day being lethal in dams. Rat maternal drug transfer is 20-40% whereas in rabbit it is only 2%.
Similarly, in an oral mouse Segment II study testing 8, 80, 800 mg/kg/day, maternal toxicity is not evident but skeletal malformations are increased at 80 and 800 mg/kg/day by 6/24, 8/24 litters respectively versus 4/24 control litters. Visceral variations in 3/24 litters given 800 mg/kg/day versus 1/24 control litters were observed. A mouse developmental NOAEL= 8 mg/kg/day (or 24 mg/m^2 providing a 2X safety margin to the therapeutic dose of 20 mg/day=12 mg/m^2) was established.

Studies of lovastatin co-administered with either mevalonic acid or cholesterol appeared to attenuate the more severe fetal malformations, however some fetal skeletal toxicity is observed (wavy ribs, incomplete ossification etc.) despite the addition of mevalonate. This supports the original conclusion that the fetal findings result from disruption of cholesterol biosynthesis as an extension of the pharmacologic activity of lovastatin. Merck concludes that fetotoxic effects at maternally toxic doses of lovastatin are not a function of reduced cholesterol biosynthesis (decreased fetal plasma mevalonate). Rather they conclude that fetotoxicty at maternally toxic doses of Mevacor is a function of reduced cholesterol biosynthesis in the forestomach. HMG-CoA reductase required for mevalonate synthesis is tissue bound (endoplasmic reticulum). Hence, tissue levels of mevalonate could be different than plasma levels, as suggested by Merck's attribution of reduced rat forestomach mevalonate as causative of maternal toxicity during developmental studies.

Lovastatin	Plasma Mevalonate Levels (ng/ml)	
Dose/Route (mg/kg/day)	Maternal	Fetal
Oral 80	10	29
Oral 400	11	45
SC 12.5	8	36
SC 25	11	39

Differences in the timing of developmental processes across species is not generally addressed in interpretation of standard reproductive toxicology studies. This becomes important in regard to particular developmental events. For example, myelination occurs in the rat during postnatal weeks 2-4. The standard reprotoxicity test battery does not extensively evaluate postnatal developmental processes, particularly neurological maturation to any significant effect. The majority of myelination occurs in humans during the second and third trimester. This implies that the nonclinical animal studies with standard designs did not evaluate this process at all. Furthermore, limited first trimester clinical exposure would also not be relevant to address this potential risk. Therefore, a limited postnatal neurodevelopmental assessment following direct dosing in neonatal rats was recommended. The results of this study suggested a NOAEL of 5 mg/kg/day (20X clinical exposure following a 20 mg/day dose based on AUC) based on a delay in learning/short-term memory assessment (passive avoidance test) at 10 mg/kg/day. The

neurological evaluation was minimal and standard general toxicology endpoints were not assessed in the neonatal rat following direct dosing. The study represents the only "new" data provided by Merck which still does not significantly address the concern originally identified. Merck included a passive avoidance test as the sole measure of cognitive function in the direct dosed neonatal rat study. The Agency suggested on several occasions that a more sensitive test of learning and memory in which a learning acquisition curve can be demonstrated (e.g. complex water maze) was preferred. The neonatal rat study was designed to evaluate acute toxic effects on neurologic development, but does not assess delayed effects of a developmental insult because in a neonate, organ structure is already complete. In order to assess this, dosing would have to encompass a longer period of exposure (e.g. *in utero* through weaning).

Conclusion: Extensive reproductive toxicology studies with lovastatin performed from 1980-1999 using standard study designs demonstrate consistent findings of fetal mortality, body weight decrements, skeletal malformations, and behavioral/learning delays in the absence of maternal toxicity. Merck suggests that the skeletal malformations are a function of maternal toxicity. Based on the well established effect of statins on cholesterol synthesis and the knowledge that major neurodevelopment occurs postnatally in the rat, additional neurodevelopmental assessments of lovastatin were recommended. A limited neurodevelopmental assessment following direct dosing of neonatal rats suggests a no observed adverse effect level (NOAEL) of 5 mg/kg/day (exposure 20X a clinical dose of 20 mg/day based on AUC). This is based on a delay in a learning/short-term memory assessment (passive avoidance test) at 10 mg/kg/day. It is noteworthy that the 20X exposure multiple is calculated from directly dosing neonates and obtaining actual plasma levels in the neonates whereas earlier developmental studies directly dosed the mothers and based exposure levels on maternal plasma levels, hence the slight difference in safety margins. This neonatal rat study was designed to evaluate an acute developmental insult and is limited in the scope of its evaluation to address the developmental concerns outlined.

Recommendations: Approvable, pending adequate labeling to identify the potential developmental risk to women of child bearing potential

Labeling with basis for findings: see clinical review

X. APPENDIX/ATTACHMENTS:

Abbreviations: NOAEL-no observed adverse effect level, GD-gestation day, AUC-area under the curve, NOEL-no observed effect level, CHD-coronary heart disease, NEJM-New England Journal of Medicine, SC-subcutaneous, OTC-over the counter.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Karen Davis-Bruno
1/28/05 10:33:54 AM
PHARMACOLOGIST
AE pending adequate labeling to address potential developmental risk in females of CBP

Joint Meeting of the Nonprescription Drugs Advisory Committee and the Endocrinologic & Metabolic Drugs Advisory Committee
January 13-14, 2005

This is the final report of the Joint Meeting of the Nonprescription Drugs Advisory Committee and the Endocrinologic & Metabolic Drugs Advisory Committee held on January 13-14, 2005. A verbatim transcript will be available in about 2 weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder05.html#NonprescriptionDrugs

All external requests should be submitted to the Freedom of Information office.

The Nonprescription Drugs Advisory Committee and the Endocrinologic & Metabolic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met jointly on January 13-14, 2005, at the Versailles Ballrooms, Holiday Inn, Bethesda, Maryland.
Alastair Wood, M.D. chaired the meeting.

Nonprescription Drugs Advisory Committee (voting):
Alastair Wood, M.D. (Chair), Neal Benowitz, M.D. , Terrence F. Blaschke, M.D., Leslie Clapp, M.D., Ernest B. Clyburn, M.D., Frank F. Davidoff, M.D., Jack E. Fincham, Ph.D., Ruth M. Parker, M.D., Sonia Patten, Ph.D. [CR], Wayne R. Snodgrass, M.D., Ph.D., Robert E. Taylor, M.D., Ph.D., F.A.C.P., F.C.P., Mary E. Tinetti, M.D.

Endocrinologic & Metabolic Drugs Advisory Committee (voting):
Sonia Caprio, Thomas O. Carpenter, M.D., Dean A. Follmann, Ph.D., Michael R. McClung, M.D., David S. Schade, M.D., Morris Schambelan, M.D., Nelson B. Watts, M.D., Margaret E. Wierman, M.D., Paul D. Woolf, M.D.

Special Government Employee (SGE) Consultants (voting):
Richard A. Neill, M.D., James Schultz (patient representative)

Government Employee (voting):
Susan Makris, Ph.D.

Industry Representative (non-voting):
Steven W. Ryder, M.D.

FDA Speakers:
Karen Davis-Bruno, Ph.D., Charles Ganley, M.D., Michael Koenig, Ph.D., Mary Parks, M.D., Laura Shay, RN, M.S., C-ANP, Daiva Shetty, M.D.

FDA Participants:
Jonca Bull, M.D., Charles Ganley, M.D., John Jenkins, M.D., Robert Meyer, M.D., David Orloff, M.D., Mary Parks, M.D., Curtis Rosebraugh, M.D.

Open Public Hearing Speakers (January 14, 2004):
James McKenney, PharmD - National Lipid Association
Suzanne Hughes MSN RN - Preventive Cardiovascular Nurses Association
Stewart S. Levy, R. Ph. - Impact Health
Robin Edison, M.D., MPH
Dr. Boisey Barnes - Association of Black Cardiologists, Inc.
Sidney M. Wolfe, M.D. - Public Citizen's Health Research Group
Alice Rein, M.S. - National Consumer League
Penny M. Kris-Etherton, Ph.D., R.D. - Penn State University
William L. Greene, Pharm.D., BCPS, FASHP - American Society of Health-System Pharmacists
Tracy Hankin - WebMD

Bob Dufour - Walmart
Jan Engle, - American Pharmacists Association
Laurie Tansman - Mt Sinai NYU Health
Christopher Maus - Lifestreams Technologies, Inc.

These summary minutes for the January 13 and 14, 2005 of the Joint Meeting of the Nonprescription Drugs Advisory Committee and the Endocrinologic & Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on February 3, 2005.

I certify that I attended the January 13 and 14, 2005, Joint Meeting of the Nonprescription Drugs Advisory Committee and the Endocrinologic & Metabolic Drugs Advisory Committee of the Food and Drug Administration meeting and that these minutes accurately reflect what transpired.

_____//S//_____
Hilda F. Scharen, M.S.
Executive Secretary

_____//S//_____
Alastair Wood, M.D.
Chair

On both days, the committees considered the safety and efficacy of new drug application (NDA) 21-213, proposing over-the-counter (OTC) use of Mevacor 20 mg a day, (lovastatin), Merck & Co., Inc., to help lower LDL "bad" cholesterol, which may prevent a first heart attack.

Alastair Wood, M.D. (Committee Chair), called the meeting to order at 8:00 a.m. on January 13, 2005. The Committee members, consultants, and FDA participants introduced themselves. The conflict of interest statement was read into the record by Hilda Scharen, M.S. The agenda proceeded as follows:

Introduction Regulatory History and Overview of Current Proposed OTC Program	Mary Parks, M.D., Deputy Director Division of Metabolic and Endocrinologic Drug Products Office of Drug Evaluation II
Sponsor Presentations:	
Introduction	Edwin Hemwall, Ph.D., Vice President Worldwide Regulatory and Scientific Affairs Johnson & Johnson / Merck Consumer Pharmaceuticals
Rationale for OTC Lovastatin	Richard Pasternak, M.D. – VP, Clinical Research Merck Research Labs
Mevacor OTC Self Management System	Jerry Hansen, RPh - Vice President Business Development and Consumer Research, Johnson & Johnson / Merck Consumer Pharmaceuticals
Actual Use Study Results	Robert Tipping, M.S. Director, Biostatistics Merck Research Labs
Medical Perspective and Conclusion	Jerome D. Cohen, M.D., FACC, FACP Professor of Internal Medicine/Cardiology Director, Preventive Cardiology Programs St. Louis University Health Sciences Center

FDA Presentations:

Reproductive and Fetal Toxicity	Karen Davis-Bruno, Ph.D. Division of Metabolic and Endocrinologic Drug Products Office of Drug Evaluation II
Label Comprehension Study	Laura Shay, RN, M.S., C-ANP Division of Over-the-Counter (OTC) Drug Products Office of Drug Evaluation V
CUSTOM – Actual Use Study	Daiva Shetty, M.D. Division of Over-the-Counter (OTC) Drug Products Office of Drug Evaluation V
Nonprescription Simvastatin in the United Kingdom	Michael Koenig, Ph.D. Division of Over-the-Counter (OTC) Drug Products Office of Drug Evaluation V

The meeting was adjourned at approximately 5:20 p.m. on January 13, 2005.

Alastair Wood, M.D. (Committee Chair), called the meeting to order at 8:04 a.m. on January 14, 2005. The conflict of interest statement was read into the record by Hilda Scharen, M.S. The agenda proceeded as follows:

Open Public Hearing Presentations

Questions to the Committee:

1. Taking into consideration the efficacy data from the AFCAPS/TexCAPS and EXCEL studies, plus any additional information provided by the sponsor, please respond to the following questions:

a. Does the proposed target population merit treatment with a statin to lower cholesterol and thereby reduce heart disease risk?

Yes: 24
No: 0
Abstain: 0

Discussion: The subcommittee agreed the proposed target population would benefit from treatment with a statin to lower cholesterol and reduce heart disease, along with improved diet and exercise.

b. Has the sponsor provided adequate rationale for the use of a fixed dose of lovastatin 20 mg to lower cholesterol and heart disease risk in this population? Is this an effective dose to reduce cholesterol in this population?

Yes: 24
No: 0
Abstain: 0

Discussion: The subcommittee discussed that this study assumes adherence to the label. In addition, the members emphasized that there is not enough data, especially for Over-The-Counter use, of the efficacy of a 20mg dose versus usual care.

2. Lovastatin and other statins cause elevation in hepatic transaminase serum levels of unknown clinical significance in individuals with normal baseline hepatic function.

a. Does the Committee think that pretreatment baseline liver function tests are required prior to starting lovastatin therapy?

Yes: 0
No: 24
Abstain: 0

b. Are the liver function tests necessary during administration?

Yes: 0
No: 24
Abstain: 0

Discussion: Some members underlined that baseline liver function tests (LFT) should be required before administration of lovastatin 20 mg. Other committee members also felt that LFT should be required during therapy, for continued safe use of the drug.
The committee members generally found that the risk of liver toxicity with statins seems to be similarly low and were not excessively concerned about patients with undiagnosed liver problems taking Mevacor Daily.

3. Statins have been associated with the development of serious muscle toxicity. Furthermore, drug-drug interactions with lovastatin may increase the risk of muscle toxicity. Is the risk of muscle toxicity with lovastatin 20 mg acceptable for an OTC drug; as applied to the population indicated in the label?

Yes: 24
No: 0
Abstain: 0

Discussion: The subcommittee argued that the study indicated problems in the self-selection of patients for use of lovastatin, which may cause some safety concerns.

4. Lovastatin and other statins are currently labeled as Pregnancy Category X (the drug should not be used during pregnancy). Have you heard data that suggests to you that the drug is not so potentially toxic to the fetus to prevent its marketing OTC under any circumstance?

Yes: 18
No: 5
Abstain: 0

Is the label adequate for this group?

Yes: 0
No: 24
Abstain: 0

Discussion: The subcommittee discussed that the CUSTOM study is not a good representation of the general population, especially for women of child-bearing age who might take Mevacor. Some members indicated that the drug comparison study included drugs not comparable to Mevacor. The members added that some of the drugs used in this study are not Over-The-Counter and are used only under Physician's care, such as Epinephrine.

The members highlighted that the label advising against use of the drug during pregnancy or while trying to become pregnant, should include consequences, such as how significant the risk of damage may be to the fetus. In addition, the members were concerned that women who were unaware that they were pregnant would take Mevacor and possibly damage the developing fetus.

The Committee recognized it is difficult to estimate the risks of birth defects, as well as be able to correlate animal drug studies to humans. The members concluded that the data presented is not conclusive enough to extrapolate risk versus benefit to an OTC situation.

Taking into consideration the results from the CUSTOM actual use study:

5. Does the frequency of appropriate self-diagnosis and self selection support the conclusion that lovastatin 20 mg can be used safely and effectively in the OTC setting? Please describe which analysis influenced your decision.

Yes: 5
No: 18
Abstain: 0

Discussion: The members felt they did not have insight into the population that self-selected and used inappropriately; this information would be critical as product understanding comes from the users. Thus, the committee added that the label comprehension study should be made a part of the actual use study.
Some members emphasized that the information needed to self-manage, while taking Mevacor, is too complex to reduce to an understandable level for the general population. In addition, the members discussed that the CUSTOM study literacy level was higher than that of the general population.

The committee indicated that there is a need for more organized tests to test what is critical information and reduce confusion. The members concluded that the self-diagnosis results of the CUSTOM study did not support that lovastatin 20 mg can be used safely and effectively in the OTC setting.

6. A high percentage of study subjects in the CUSTOM actual use study relied upon a physician for correct self-selection and/or self-diagnosis.

a. Do you expect the general population will have this degree of health care provider interaction?

Yes: 2
No: 16
Abstain: 5 (Those who abstained from voting felt that there was not enough information available to answer this questions.)

b. Do the CUSTOM actual use study results support a conclusion that individuals can use lovastatin 20 mg safely and effectively in the OTC setting without the guidance of a physician?

Yes: 3
No: 20
Abstain: 0

Discussion: The committee members pointed to the fact that close to two-thirds of the patients were not among the intended population for treatment with the statin and that a high percentage of patients relied upon a physician for correct self-selection and/or self-diagnosis to start treatment with lovastatin.

Some members abstained from voting because they did not feel they had enough information to extrapolate the degree of interaction of subjects with their health care provider to the general population.

Although the committee members criticized the CUSTOM study, they praised Merck for its efforts to bring the statin to Over-The-Counter and encouraged the company to continue its efforts, as a means to address the enormous and growing cardiovascular public health problem in the country.

The committee concluded that based on patients' inability to self-select for treatment and to comply with long-term use and testing, individuals could not safely and effectively use lovastatin in the OTC setting.

7. Do the results regarding self management (i.e. user behavior after the initiation of treatment) raise any concerns about the safe and effective use lovastatin 20 mg in the

OTC setting? If yes, what are the concerns? Please consider in your discussion: monitoring LDL-C, physician interaction, new risk factors or medication after initiation of therapy.

Yes: 23
No: 0
Abstain: 0

Discussion: The subcommittee expressed some concerns of potential drug interactions with the use of lovastatin. In addition, the members the study presented was not conclusive enough to indicate adequate self-monitoring of individuals taking 20 mg lovastatin. Some members added that patients with low income and no insurance would be unlikely to get LDL tests, which would make it difficult to recognize any new conditions these individuals may have.

Based on all the information provided:

8. Should Mevacor OTC be marketed OTC for the proposed target population?

a. If no, why not?

b. If yes, why?

c. If yes, do you think Mevacor OTC is safe and effective for use in the OTC setting without the "self-management system"?

Yes: 3
No: 20
Abstain: 0

Discussion: The members argued that making Mevacor more easily available would help get needed treatment to millions of Americans at moderate risk of heart disease that needed to lower cholesterol levels.

The committee felt that the safety and benefits of Mevacor are well-established, but was concerned that the wrong people might take it if available in an OTC setting, especially after an aggressive advertising campaign.

The members expressed worry that patients will skip necessary doctor visits or inaccurately determine the drug is for them, while forgoing important advice about changing diet and exercise in order to control their elevated level of cholesterol.

The committee concluded that the Health Care System is currently not designed for such OTC use of statins and individuals could not operate in this system effectively. The concerns expressed by the members stemmed that this may set precedence for approval for other “silent” diseases drugs, such as anti-diabetic or high blood pressure drugs, to go OTC while the infrastructure is not adequate to support this.

Some committee members expressed interest in seeing an in-between option in an OTC setting, where patients could buy the drug without a prescription but only after speaking with a pharmacist; such an option is available in Britain, where a similar drug is being sold "behind-the-counter”.

Finally, the committee praised Merck in the efforts to address the needs of individuals without health insurance, who should also have the right to have treatment with statins. In addition, the members felt that FDA and Merck need to work together to bring more effective and cost effective drugs to an OTC setting.

The meeting was adjourned at approximately 3:00 p.m. on January 14, 2005.

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-213

Food and Drug Administration
Rockville MD 20857

OCT 6 2000

Merck & Co.
Attention: Edwin L. Hemwall, PhD
Vice President, Regulatory Affairs
Sumneytown Pike BLA-33
West Point, Pennsylvania 19486

Dear Dr. Hemwall:

Please refer to your new drug application (NDA) dated December 10, 1999, received December 10, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mevacor® CC (lovastatin) Tablets, 10 mg.

We acknowledge receipt of your submissions dated January 7, February 1, 2, 11, 18 (3), and 25, March 2, 3, 7, 13 (2), 15, 16, 20, 23 (2), and 29 (2), April 3 (3), 5 (fax), 10 (2), 11, 13 (2), and 18 (2), May 1, 2, 17 (3), 19, 23, 30, and 31, June 12 (2), July 6 and 19, August 11, 15, 16, and 22, and September 11, 20, and 29, 2000.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). This application is not approvable due to the following deficiencies.

1. Neither the rationale for treating the proposed target population with Mevacor 10 mg in the over-the-counter (OTC) setting, nor a favorable benefit/risk ratio for such treatment has been adequately established. Furthermore, the ability of consumers to appropriately self-select and to adequately comply with chronic Mevacor therapy without the intervention of a physician has not been demonstrated. A summary of the basis for these conclusions follows.

   a. Current National Cholesterol Education Program (NCEP) Guidelines recommend diet and lifestyle modification as initial therapy for lowering cholesterol levels in the population of patients that you have proposed to target for OTC marketing. The patient's physician may individualize the treatment recommendations for this population of patients to include drug therapy as warranted. Decisions regarding drug therapy of hypercholesterolemia are individualized by the physician based on an assessment of the patient's overall risk of cardiovascular (CV) disease, a determination that the patient's cholesterol levels are too high considering that risk, an assessment of the benefits and risks of a drug or a combination of drugs for a given patient, and with specific goals of therapy defined in advance (i.e., LDL cholesterol [LDL-C] and total cholesterol [TC] levels). Any recommendations for OTC use of Mevacor must implement appropriate principles to allow consumers to safely and effectively use Mevacor as part of an overall program to reduce their

risk of CV disease in the OTC environment. You have not provided sufficient evidence to either establish that Mevacor can be used by consumers in accordance with the current treatment paradigm (as reflected in NCEP guidelines) in the OTC environment or to establish the appropriateness of a new treatment paradigm that is likely to give greater emphasis to primary drug therapy over the usual "stepped care" approach of diet and lifestyle modification, followed by drug therapy, if warranted, in the population targeted.

b. A clinical cardiovascular benefit of Mevacor 10 mg has not been established in controlled clinical trials in the proposed OTC target population. You have not provided adequate information to support extrapolation of the clinical CV benefit of Mevacor observed in controlled clinical trials in higher-risk populations to the lower-risk population targeted for OTC marketing. Your proposed extrapolation of clinical CV benefit from a subgroup of patients in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAP/TexCAPS) to the proposed OTC target population is problematic due to the differences in HDL-cholesterol (HDL-C) levels in the two populations. AFCAP/TexCAPS specifically recruited a higher-risk population with below-average HDL-C levels. In contrast, the definition of your proposed OTC target population includes TC 200-240 mg/dL and LDL-C >130 mg/dL, but does not include a target HDL-C level. HDL-C is a recognized contributor to CV risk. Without data that serve to more directly measure the CV benefit of Mevacor 10 mg in the target OTC population and to establish that a clinically meaningful benefit is obtained even among the lower-risk individuals included in this population, it is not possible to conclude that the benefit/risk ratio for the proposed OTC use is favorable.

c. As noted above, one of the cornerstones of treatment of hypercholesterolemia has been individualization of therapy to reach a pre-determined treatment goal. Your proposal for OTC marketing of Mevacor 10 mg does not include a treatment goal and does not allow the consumer to individualize their treatment as needed to achieve the treatment goal without the intervention of a physician. Given the complexities of treatment of hypercholesterolemia to reduce CV risk, an OTC treatment algorithm may not be appropriate or practicable for patients across the full range of CV risk and cholesterol levels, nor across the full range of approved Mevacor dose levels. However, in order to support OTC marketing of Mevacor, you must demonstrate either that consumers can understand and adequately implement treatment to a defined goal in the OTC environment or that there is an identifiable population of consumers for whom treatment with a fixed dose of Mevacor, without titration to reach a treatment goal, would represent an acceptable standard of care.

d. You have not demonstrated that consumers can adequately comprehend the complexities of treatment of hypercholesterolemia (e.g., various types and levels of cholesterol, assessment of individual cardiovascular risk, treatment goals) or that consumers can appropriately self-select for OTC treatment and adequately

comply/adhere with the chronic therapy required to obtain a clinically-meaningful reduction in individual CV risk. In your clinical and actual use studies, there were significant problems identified with consumer self-selection, compliance, and adherence to chronic therapy, which calls into question whether many consumers would be able to use Mevacor safely and effectively to reduce their individual CV risk without intervention by a physician.

e. Mevacor has been associated with elevations in hepatic transaminases, rare reports of hepatic failure, and rare reports of rhabdomyolysis. The approved package insert for Mevacor for prescription use recommends monitoring of hepatic transaminases at specified intervals. You have not provided adequate justification for deleting the recommendation for hepatic transaminase monitoring for Mevacor 10 mg when used in the OTC setting while these monitoring recommendations remain in the prescription labeling. Furthermore, you have not adequately demonstrated the ability of consumers to comprehend the risk of serious muscle toxicity associated with the use of Mevacor and the ability of consumers to recognize early symptoms of muscle toxicity and to appropriately discontinue Mevacor treatment and seek medical attention. These safety concerns need to be further addressed in support of any proposed OTC marketing of Mevacor.

f. Lovastatin is extensively metabolized by cytochrome P450 3A4. Concomitant use of Mevacor with one of the many drugs that inhibit this metabolic pathway can result in increased circulating levels of parent lovastatin and its metabolites and increase the risk for serious muscle toxicity. You have not adequately demonstrated the ability of consumers to comprehend the risks associated with concomitant use of Mevacor with these numerous interacting drugs, nor have you demonstrated the ability of consumers to avoid concomitant use of Mevacor with one or more interacting drugs without the intervention of a physician. Adequately addressing this important safety issue is critical to any proposal for OTC marketing of Mevacor.

g. Many of the consumer education programs and materials that you have proposed for use after approval of OTC marketing of Mevacor 10 mg have not been adequately tested to evaluate their ability to aid consumers in the safe and effective use of Mevacor. You have not adequately addressed how consumers will access accurate cholesterol testing in the OTC setting, nor have you adequately defined and tested the types of support that will be available to the consumer at the retail outlet to assist in the purchase decision and to encourage appropriate follow-up testing to facilitate the safe and effective use of Mevacor.

h. You have not adequately addressed the risks to the fetus of potential Mevacor use by women who are pregnant or of childbearing potential in the OTC setting. Mevacor is currently labeled as Pregnancy Category X, which is a major concern in considering the proposal for OTC marketing. The battery of reproductive toxicity tests conducted for lovastatin was inadequate to assess for potential drug effects on neuronal development processes that occur postnatally in the rat (e.g.,

myelinization). This is important for this category of drugs given their known effects on cholesterol synthesis. The CDER Reprotoxicity Committee has reviewed the findings from your studies. Additional postnatal development studies are recommended to support proposed changes to the pregnancy category for Mevacor and/or OTC marketing.

2. The proposed product name, Mevacor CC, is not acceptable. You should submit a new proposed product name that does not include the "CC" suffix.

3. During a recent inspection of your Rahway, New Jersey, manufacturing facility, a number of deficiencies were noted and conveyed to you by the investigator. A satisfactory inspection is required before this application may be approved.

Your complete response to this letter should include a safety update as described in 21 CFR 314.50(d)(5)(vi)(*b*). Please provide updated information as listed below. The update should provide the data lock date and cover all studies, both U.S. and foreign, and all uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action, FDA may proceed to withdraw the application. Any

amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Margaret Simoneau, R.Ph., Regulatory Project Manager, at (301) 827-6418.

Sincerely,

Robert J DeLap

Robert DeLap, M.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

John K. Jenkins, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-213

Merck & Co., Inc.
Attention: Edwin Hemwall, Ph.D.
Vice President, Global Regulatory Affairs
Sumneytown Pike, P.O. Box 4
BLX-29
West Point, PA 19486

Dear Dr. Hemwall:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mevacor CC (nonprescription lovastatin) 10 mg tablets. We also refer to your February 19, March 4, and May 10, 2002, submissions containing proposals for a nonprescription (over-the-counter, OTC) form of lovastatin for treatment of mild- to- moderately elevated cholesterol.

We have reviewed the referenced material and have the following comments and recommendations to your questions proposed on February 19, 2002.

1. **Section A of this background document describes 3 alternative paradigms: (1) Option 1a. LDL + 2 risk factors; (2) Option 1b. TC + 2 risk factors; and (3) Option 2, the Framingham approach.** ***Are all 3 alternative paradigms acceptable to FDA? If not, does the Agency have a preference for one of the risk factor approaches?***

   The treatment paradigm for the OTC Mevacor program should incorporate similar recommendations for treatment of hypercholesterolemia under the Rx Mevacor program. As such, the inclusion of LDL-C as part of the selection criteria and treatment goal is essential. An option which substitutes total-C for LDL-C, although more consumer-friendly, would not be considered an acceptable clinical approach for determining when to initiate drug therapy. The use of a Framingham Risk Score calculation would, in contrast, be too complex for consumer use.

2. **Regarding the Risk Factor Approach (Option 1a or 1b):** ***If this approach is acceptable, can TC cut points be used as a surrogate for LDL in order to minimize consumer confusion? If LDL cut points are preferred as entry criteria, can treatment goals be expressed using TC?***

Refer to question 1.

3 Regarding the Framingham approach (Option 2): ***If this approach is acceptable, can a substantial number (40% according to NHANES) of consumers qualified by Risk Score (10-20% / 10-year) have an LDL <130 mg/dL before starting treatment? Is a treatment goal based upon TC acceptable?***

Refer to question 1.

4. Are the "Do Not Use", "Check with Doctor before using" reasons acceptable? Are there any additional criteria that should be included?

The reasons are acceptable, but the OTC label should warn the consumer not to use the product if he/she has experienced a muscle problem from any cholesterol lowering medicine.

5. The Framingham approach is best carried out through use of a calculator-like device which would be made available on the retail shelf at the point of purchase and not part of each individual package. ***Is this acceptable to the Agency?***

Refer to question 1.

Comments on Proposed Actual Use Study:

a. To create the most naturalistic testing situation:
   - If advertisements at the point of purchase will influence consumers to use the product, then these same advertisements need to be used if the product is marketed OTC.
   - Consumers should not be told to bring their most recent fasting cholesterol numbers to the study site at the time they make their appointment.
   - Consumers should not be told to return for follow-up visits when they need to purchase additional medication or a follow-up cholesterol test. Instead they should be advised to follow the directions on the label and should be informed that they can purchase more medicine at the study site.
   - Compensation should not be used as an incentive for follow-up visits.
   - Study drug should not be collected during study visits.
   - Cholesterol should be checked on all participants after they self-select so self-selection can be validated.
   - Initial questions at the follow-up visits should be scripted and open-ended so as to enable us to learn if consumers are thinking in terms of important medical concerns.
   - Investigators acting as surrogate pharmacists at the study site should be located "behind-the-counter" like pharmacists would be in a pharmacy.
   - Directions about fasting prior to having blood drawn to measure cholesterol should be on the drug label and on the cholesterol-testing machine. This should not be discussed with the participant. Whether participants fast prior to testing the cholesterol should be a study endpoint.

b. The sponsor should provide data supporting the safety of Mevacor CC in consumers with elevated baseline LFTs and/or consumers who develop LFT elevations while on therapy. LFTs should be performed at Visit 1 and at the last visit.

Comments on Proposed Label Comprehension Study:

Label

The label must be in Drug Facts Format. Consider making the following label modifications and testing them for comprehension.

- The label should have a warning like "Do Not Use: if you have experienced a muscle problem from any cholesterol lowering medications."
- Inform consumers how frequently they need to test their cholesterol while taking Mevacor CC.
- Inform consumers about the need to fast before having the cholesterol tested.
- Convey the importance of family history in a first degree relative as a risk for heart disease without listing age.
- In the "Use" section, indicate that persons using the product must meet certain criteria demonstrated by the wheels and by the "Who should use" section, as well as the warnings section.
- There are two items about not taking the product with prescription medicines without checking with a doctor. One is more general, for any prescription medicine, and the other is for medicines to lower cholesterol. These two items could be combined.
- In the "Who should use section"
  - Highlight in some way "to all 4" when describing who can use the product
  - In the first panel, change the blue "or" to "and"
  - Change "must not use" to "Do not use"
  - In the third panel, change "father/brother" to "father or brother." Do the same for "mother/sister."
  - In panel 4, state "…you must be free of all conditions listed in red in the Warnings section above." Then list all warning items that are contraindications in a highlighted form.
  - Change "who should use" to "who can use."
- Keep the language on the label consumer friendly. For example:
  - Simplify wording to change "medication" to "medicine."
  - In the Directions section, change "immediately" to "right away."

Study Design:

Before asking participants if they might be interested in the study product, the interviewer shows them a product description that talks about the once-a-day way to lower cholesterol, which can significantly reduce the risk of heart disease. It mentions that the dose is one pill a day.

We do not believe it is necessary to have the product description step in the study, as it provides information about the product that does not come from the label. However, if the sponsor believes it is important to keep, because its use weeds out participants who are less serious about buying the product, then this information should be less promotional. It should not include dosing information or any other information about which participants will be asked later.

We do not believe it is necessary to analyze responses by education, income and exercise habits, as the sponsor suggests is possible. We are most concerned about responses from the representative and low literate groups, and education and income are surrogates for that measure.

It would be useful to use the exercise habits to determine if participants answered correctly that they could use the product, as it is intended only for persons for whom exercise and diet have not worked.

Sample Screening Questionnaire

The sponsor uses a non-threatening way to obtain participants' age, by first asking year of birth, and if that is refused, asking for an age range.

The instructions direct the interviewer to skip the question about needing to wear reading glasses if the participant is already wearing glasses. We recommend asking this question of all participants, as some may be wearing glasses for distance and may need other glasses for reading.

Main Questionnaire

The interviewer is directed to point out the wheels on the carton to participants, as well as the top, bottom, back and front of the carton. Interviewers then tell participants to feel free to use the wheels. It would be better for interviewers not to be so directive. Rather than pointing out various features of the carton, interviewers should tell participants to read the package as they would if they were in a store thinking of buying the product. This is because we want to know how well the carton communicates on its own.

Because the carton is so complicated and innovative, and participants may not understand what is to be expected of them, we recommend the interviewer state something like the following: "When I come back, I will ask you some questions about the product. You will be able to look at the carton to answer my questions." Otherwise, participants may spend time trying to memorize the information in a way they would not normally do in a store, anticipating they may not have the label for reference during questioning.

Q.4a asks if the participant used the wheels. If not, the interviewer states "I will give you a minute or two to use the wheels." We believe directing them to use the wheels will not provide us with information about how well the product package communicates to the ordinary user. In an actual purchase situation, consumers will not be told to use the wheels. Perhaps at the end of the interview, participants could be asked if they used the wheels, and those who did not use the wheels could be asked why they didn't use the wheels.

Questions 6a and 6c are leading. They ask if, according to the label, if there is anything a person must try or must know before beginning to use the product. It would be less leading to ask scenario questions giving situations in which a person has or has not done or learned the appropriate things before using the product. For example, one scenario might give an example of a person with a particular total cholesterol level and particular triglycerides. Can that person use the product? Why or why not?

Q.6 about whether there is something a person must try or know before using the product should not come before the self-selection question. If Q. 6 comes before the self-selection question, it induces participants to think about what issues they must consider when they reach the self-selection question that comes next. The sponsor has said that participants tend not to answer the self-selection question accurately if it comes very early in the questioning because participants do not understand that the question is meant to apply to them, personally. However, the possible bias induced by asking Q. 6 first may negate our ability to conclude how well the label alone helps participants make a decision about self-use.

The sponsor is testing several alternative ways to ask the self-selection question. This is commendable. We prefer that the best alternative is used and that Q.6 comes **after** the self-selection question, not before it. Later in the questionnaire, participants who selected inappropriately are asked why they did so, and that should provide information about the causes for incorrect responses to the self-selection question to help us determine if the label is unclear.

Q. 7e asks participants if they would talk to their doctor before use if they had not already volunteered that they would do so. Because this question is leading, responses may be of questionable value.

There are several sets of scenario questions. The first set, at Q.10, deals with requirements for using the product. Of the 5 scenarios, the first presents a case in which the person could use the product immediately. The second requires the person to get more information or to talk to a doctor first, and the last three require not using the product. We suggest that scenario K include the mention of a risk factor, so the only reason the person cannot start using the product immediately is lack of knowledge of her cholesterol. We also suggest that the heading for the column that says "Do not use now, this person needs to get numbers or talk to doctor first" should be changed to "Do not use now, this person needs more information or must talk to the doctor first." This recommendation will remove the reference to numbers in the heading, which is a clue to participants that they must know their numbers. Scenario T should mirror the other ones in saying there are no other reasons not to use this product starting today.

In this group of scenarios, there are several important issues that are not covered. These include being too young, triglycerides >200, allergy, pregnant or breast feeding, LDL above 171, history of stroke, high blood pressure, or diabetes, or have not tried diet or exercise. We believe most of these issues should be covered by the questions. One option would be to create more scenarios to test these issues. Another would be to include them, along with some false issues, into a revised Q.11 (See suggestions for revision, below). Perhaps some false risk factors should be added to the scenarios in Q.10, such as the father having high blood pressure before age 55, or if age is removed from the label, perhaps HDL>40 and no mention of smoking or other risk factors.

Q.11 presents a list of three types of people who should not use the product right away and asks if they can use the product right away. It also asks if "none of the above" would be correct. If someone knows that 2 of the 3 cannot use it, they will then realize they must answer "none of the above" even if they did not realize the third category could not use it. This type of question would be better asked with a list of types of persons who could and could not use the product

right away, with the participant answering for each one if they could or should not use it immediately.

The second set of scenario questions (Q. 12a) has four questions that ask about use by people taking various medications and supplements. The third set (12b) asks about taking the product with other health conditions. Two of these do not seem believable—using new reading glasses and having warts. These should be changed to something more believable but that would permit use of the product. Something chronic or systemic would work better.

We suggest the wording in Q. 13a say "You can" refer to the package, rather than being more directive and saying "you should" refer to it.

There is a series of questions asking directly and indirectly if the package says certain things. All of these are about information that **is** on the package. We suggest a few questions interspersed about information that **is not** on the package to avoid an acquiescence bias. For example, there could be a question as to whether the package says how many months or years you can use the product before something stronger is needed. Another might ask if the label says when to increase the dose. Other questions about information not on the label could be asked.

We suggest changing Q.l3g to another format. This question is about the best time to take the medicine. It is now basically a yes/no format. It would be better as a scenario or alternatively, it would work better to give a list of times and ask which are the best times to take it. Participants may choose more than one response and one choice would be that any time is just as good as another. If the format is not changed, we suggest the first part of the question not ask "Can someone take Mevacor OTC at any time…." They **can** take it at any time. The issue is the best time.

Q.14a is, again, somewhat leading. It asks if the package says anything about how long it takes for a person to see the full effects. It would be better to break this into several scenarios in which a person didn't see effects at different intervals and ask what should be done. Some intervals would be before the period on the label, and some after. Participants should be asked what the person should do.

Q. 15, another leading question, asks if the package says what a person needs to do to track progress. Again, this would be better asked in scenario questions about the need for follow-up testing. These scenarios could substitute for the subparts of Q.16 about when to get testing. Similar scenarios could be used to determine if participants understand what the target cholesterol should be to determine if the product is working.

The next set of scenarios is about situations in which the person should stop using the product. Scenario E about a person using Vaseline for dry skin is not very believable. Something else should be used, such as a non-prescription medicine. Item R is about a person whose LDL is 165 after using Mevacor OTC. It is not clear which answer should be checked for this one—continue to use the product and talk to the doctor, or stop use and talk to the doctor. If both are correct, scoring must take that into account.

Q.18 and later ask for demographic and medical information related to whether or not the person can use the product.

Q. 35b asks if they know their blood pressure and then asks if it is high, borderline high, or normal. Some people may know their numbers but may not know which category they are in. They should be given the option to give the numbers, and interviewers should be trained to write them correctly.

Q.38, about income, is not needed for Agency purposes, nor is Q. 39, about computer use. The sponsor had suggested using income and education as bases for further analyses, but such analyses are not necessary

Q. 40a says "According to the questions you answered earlier, Mevacor OTC is not right for you because (reason)." We suggest adding a sentence here such as the following: "Yet, when I asked if you yourself could immediately begin using it, you said "yes." We suggest that participants be permitted to look at the package in giving their reasons rather than asking them, as is done in Q. 40b and 41b, to rely on their memory. They may be able to point to specific parts of the label that may have confused or misled them.

If you have any questions, call Margaret Simoneau, Regulatory Project Manager, at (301) 827-6411.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Orloff

6/4/02 05:52:13 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-213

Merck and Co., Inc.
Attention: Florence F. Vickers, Ph.D., F.C.P.
Director, Worldwide OTC Regulatory Affairs
Sumneytown Pike, P.O. Box 4, BLX-29
West Point, PA. 19486

Dear Dr. Vickers:

Please refer to your new drug application (NDA) dated December 10, 1999, received December 10, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mevacor Daily (lovastatin) Tablets, 20 mg.

We acknowledge receipt of your submissions dated August 24, September 20, October 1, 8, 15, and 18 (2), November 1, 9, 11, 16, and 23, and December 2, 9, and 16 (5), 2004, and January 5, 7, 10, 11, and 20, and February 3 and 8, 2005.

The August 24, 2004, submission constituted a complete response to our October 6, 2000, action letter.

We have completed our review and find the information presented is inadequate. You have not provided sufficient evidence that you have defined labeling, packaging, and marketing proposals that would be sufficient to ensure that OTC consumers could properly assess the benefits, the risks, and the correct circumstances of use for Mevacor OTC. Furthermore, your overall program provides inadequate assurance that OTC consumers can successfully self-manage the complexities of treatment and follow up of the chronic, asymptomatic target condition in order to prevent cardiovascular disease. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

1. The results of the label comprehension and actual-use studies demonstrate that, as a whole, consumers did not correctly self-select use of the product based on the labeled criteria. While you provided evidence that the majority of the non-purchasers in the actual-use study made correct decisions not to start therapy, the majority of purchasers did not properly self-select. Your analysis, of self-selection designated subjects who purchased and used Mevacor OTC (i.e., USERS), considered self-selectors as having been correct if they fit the labeled criteria or a physician told them they could use Mevacor OTC. Using

this definition, only half of the USERS selected correctly. However, most of these USERS were assisted by a physician and did not fit the labeled criteria, suggestive that with the current proposed labeling, appropriate use of the product still requires a learned intermediary in many instances. If the stricter definition, requiring that patients fit all labeled criteria, is used, only ten percent of subjects self-selected correctly. There were few or no data collected to permit an understanding of why subjects who failed to self-select correctly chose to ignore the labeled criteria. Such data might have provided a basis for understanding why a significant proportion ignored fairly straight-forward criteria, such as age. It is possible that consumers did not understand the relevance of the labeled eligibility criteria to the potential benefits of using the product. Alternatively, they may have simply chosen to ignore the labeled eligibility criteria because of preconceived beliefs that lower cholesterol would benefit them, while ignoring or not recognizing the potential risks of use.

If you chose to continue to pursue OTC use for Mevacor, you should conduct a further self-selection/use study or studies to demonstrate that consumers can make decisions with an understanding of their likelihood of benefits weighed against the risks of using the product. We would encourage you to develop a simpler label that conveys benefit with long-term use for the labeled population (based on eligibility criteria), the likelihood of lesser a benefit if the criteria are not met (including a lower benefit than if the patient is properly treated for those with high baseline LDL-C or who inadequately respond to the Mevacor dose) and risks for serious adverse events. You are encouraged to develop this label through appropriate label comprehension studies before conducting a self-selection/use study. For the self-selection/use study, we encourage you to compare the new label against the label used in the Custom Study. Additionally, if you deviate from the Drug Facts labeling format requirements, you will need to provide justification for the deviation.

2. The actual use study data submitted suggest that most, but not all, subjects made satisfactory decisions with regard to the use of the product (after self-selection). This was particularly evident for the percentage of USERS who had their LDL-cholesterol checked (approximately 70%) and the percentage who made a correct decision on whether to continue use of the product (approximately 75%). Whether these decisions would hold in the current medical environment where cholesterol testing is not readily available is not clear.

   Amongst the concerns arising from these data, there is one area pertaining to use of the product that needs improvement in particular. In the Custom Study, only 75% of subjects who developed muscle pain made a correct decision about use of Mevacor OTC. Serious muscle toxicity is perhaps the greatest risk of toxicity for consumers using this product. Even though it is a relatively rare occurrence in the prescription setting and therefore likely would also be rare in the OTC setting, you would need to develop labeling that accomplishes a demonstrably higher rate of compliance with this important warning. If you continue to pursue OTC use of Mevacor, you will need to take additional or alternative measures in labeling that convey this important warning. Label comprehension testing should document the improvement in this labeling.

3. You have proposed the Mevacor OTC Statin Self Management System to assist the consumer in making decisions about use of the product. Some parts of the proposal fall under labeling and therefore would be mandatory for any subsequent generic programs, but other aspects of the proposal are not. As a consequence, if certain aspects of the program are deemed necessary for Mevacor OTC to be used correctly but cannot be mandated as a condition of approval, this may preclude the marketing of Mevacor OTC in the over-the-counter setting. If you continue to pursue OTC marketing, you must review all aspects of your program and determine which aspects are essential to assist the consumer in making decisions on use of the product. This information should be provided in your resubmission. While this does not preclude you from voluntarily using other mechanisms for dissemination of information that encourage correct selection and use of the product, these mechanisms cannot be essential to use if they cannot be mandated as a condition of approval.

4. You conducted alternative analyses of the self-selection results from on the Custom Study. You used these analyses to support your contention that many subjects who incorrectly self-selected were likely to obtain benefit from Mevacor OTC. Although it may be reasonable to look at these types of analyses, the validity of drawing any conclusions from them is dependent on whether they can be extrapolated to the real world setting. The consumer-based marketing of the drug will determine who considers use of Mevacor OTC. If Mevacor OTC is marketed to a broader population than indicated by the label, it is not clear that the incorrect self-selectors will be similar to those enrolled in the Custom Study. Thus, it is not clear that the incorrect self-selectors will obtain benefit as you have suggested by your alternative analyses of the Custom Study data.

   You have projected that there are approximately 7 million people in this country who fit the proposed label criteria. In your submission, you also noted that there are 57 - 65 million people who are concerned about their cholesterol and what to do about it. As part of the advisory committee discussion, the committee expressed concerns about the marketing of the product and the population likely to consider use of the product based on the consumer advertising. In the label comprehension study, 33% of the subjects made an incorrect self-selection decision. In the actual use study, 19% to 31% (depending on analysis) made an incorrect self-selection decision. If advertising and other forms of promotional communications are directed at the 65 million who are concerned about their cholesterol and not the 7 million who fit the label criteria, there may be considerable use by consumers who are likely to derive little benefit based on the percentages of self-selection errors in the two studies. It would be important for promotion efforts for this product to be directed at the population appropriate for use. Given that FDA does not have oversight over advertising of over-the-counter drug products, it is important to describe the measures you are planning to take to ensure that promotion of Mevacor OTC is directed to the targeted population based on label criteria or that you provide assurance that your promotion efforts will not engender open-market use patterns such that the results and conclusions of the self-selection studies may not be valid. For example, describe whether the label eligibility criteria will be a part of all advertising. If you chose to continue to pursue OTC use for Mevacor, we also encourage you to convey eligibility and benefit

information on the principle display panel of the Mevacor OTC package and all ancillary labeling (e.g. shelf talkers, brochures) for future submissions.

5. The prescription labeling for lovastatin recommends baseline and periodic monitoring of hepatic transaminases, as elevations exceeding three times the upper limit of normal have been observed in controlled clinical trials. While you have presented sufficient evidence that lovastatin has little to no risk of hepatic toxicity in patients with normal biochemical liver tests at baseline to warrant periodic monitoring of such patients while on lovastatin therapy, adequate data on the hepatic risk of lovastatin in patients with asymptomatic liver disease have not been provided in your resubmission for Mevacor OTC to address the safe use of this product in the nonprescription setting. This concern is not alleviated by the limited data provided from controlled clinical trials in patients with highly prevalent asymptomatic liver diseases such as hepatitis B and C and non-alcoholic steatohepatosis (NASH). Unlike the prescription setting, where a healthcare provider is responsible for making the clinical safety assessment and for obtaining baseline and post-baseline biochemical liver tests, the nonprescription use of lovastatin requires consumers to assess for themselves whether they have risk factors that would necessitate further safety laboratory testing prior to initiating therapy with lovastatin. The submitted label comprehension and actual use studies did not evaluate the ability of consumers to self-select based on risk factors or signs that might suggest a predisposition for or the existence of asymptomatic liver disease (e.g., history of blood transfusion, amount of alcohol intake). To address this deficiency, you will need to provide sufficient evidence that the risk of hepatotoxicity is minimal in patients with common asymptomatic liver diseases in order to support removal of the current recommendation to monitor hepatic transaminases or you will need to provide sufficient evidence that consumers can make clinical safety assessments of hepatic risks before initiating therapy with nonprescription lovastatin.

6. After reviewing the data provided on pregnancy risks and lovastatin, we believe that a risk of toxicity to the fetus, albeit to some extent theoretical and probably small, likely remains during the first trimester of pregnancy. We note that this risk will only be realized if early gravid women initiate therapy with lovastatin or, more likely, if women of childbearing potential initiate therapy with lovastatin and subsequently become pregnant. The proposed label for nonprescription lovastatin was inadequate in discouraging the purchase and use of this product by women of childbearing potential who are at minimal risk for cardiovascular disease, but who are at risk for inadvertent exposure during pregnancy. To address this deficiency, you will need to modify your nonprescription label and test consumer comprehension and consumer self-selection to ensure adequate consumer understanding of the risks of drug exposure during pregnancy.

7. FDA must conduct an inspection of the Merck Frosst manufacturing facility in Canada to determine satisfactory compliance with CGMPs. The facility must be found acceptable by our Office of Compliance before we can approve this application.

In addition, it will be necessary for you to submit draft labeling that has been revised in consideration of our above comments.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with the Divisions of Metabolic and Endocrine Drug Products and Over-the-Counter Drug Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Margaret Simoneau, M.S., R.Ph., Regulatory Project Manager, at (301) 827-6411.

Sincerely,

{See appended electronic signature page}

Jonca Bull, M.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Meyer
2/23/05 05:08:42 PM

Jonca Bull
2/23/05 05:12:20 PM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 25, 2005

TIME: 2:00-3:00 PM

LOCATION: 9201 Corporate Blvd. Conf. Room 200A and 200B

SPONSOR: Merck

TYPE OF MEETING: End of Review Meeting

DRUG: Mevacor™ Daily (20 mg lovastatin) Tablets

APPLICATION: Guidance/Information

MEETING CHAIR: Charles Ganley, M.D., Office Director

MEETING RECORDER: Laura Shay, Regulatory Project Manager

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD
Charles Ganley, MD	Office Director	ONP, HFD-560
Curt Rosebraugh, MD	Deputy Office Director	ONP, HFD-560
Laura Shay, RN, MS	Regulatory Project Manager	ONP, HFD-560
Andrea Leonard-Segal	Medical Team Leader	ONPDP, HFD-560
Robert Meyer, M.D.	Director	ODE II, HFD-102
Mary Parks, MD	Deputy Division Director	DMEDP, HFD-510
Daiva Shetty	Medical Officer	ONP, HFD-560
Matthew Holman, Ph.D.	Team Leader, Interdisciplinary Scientist	ONP , HFD-560
Michael Koenig, Ph.D.	Interdisciplinary Scientist	ONP, HFD-560
Margaret Simoneau	Regulatory Project Management	DMEDP, HFD-510
David Hilfiker	Associate Director of Regulatory Affairs	ODE V, HFD-105
Susanna Weiss, Ph.D.	Social Science Analyst	ONP, HFD-560
Atiar Rahman, Ph.D.	Statistician	OPSS HFD-725

EXTERNAL ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
Edwin Hemwall, Ph.D.	VP, Global Regulatory & Scientific Affairs	JJMCPC
John Irvin, MD, Ph.D.	Sr. VP, global Resear4ch & Development	JJMCPC
Florence Vickers, Ph.D.	Director, Worldwide OTC Regulatory Affairs	MRL
Jeffery Levine, MD	Sr. Director, Clinical Research	MRL
Richard Pasternak, MD	VP, Clinical Research	MRL
Robert Tipping, MS	Director, Clinical Biostatics	MRL
Brain Mayhew, BA	Regulatory Policy Analyst	MRL
Jerry Hansen, RPh	VP, Marketing, Rx-to-OTC Switch Business	JJMCPC
Stephanie Levy, MA, MBA	Director, Consumer Behavior Research	JJMCPC
Renaat Van den Hooff	President	JJMCPC

MEETING OBJECTIVES:

The meeting was requested by Merck & Co., Inc., to discuss with FDA the questions generated from the February 23, 2005, Not-Approvable Letter for Mevacor™ Daily (20 mg lovastatin) Tablets, NDA 21-213. Draft responses to the questions enclosed in the meeting background package were sent to Merck prior to the meeting. These draft FDA responses are listed below in italics. The meeting agenda consisted of further discussion based on the draft responses from the FDA.

Opening statements were made by Merck and by FDA:

Merck reported that they recognize that there were gaps in the CUSTOM actual use study, however they strongly believe in the public health benefit for having OTC access to a cholesterol lowering agent. Merck expressed concern with conducting additional consumer behavior studies because it is unrealistic to expect demonstration of a perfect consumer understanding. Merck questioned FDA on what will be considered "enough" of an understanding that may lead to approval.

FDA agreed that no study can ever demonstrate perfect consumer behavior; however, there are important safety hurdles that need to be addressed in relation to consumer behavior in the OTC setting. FDA stated that they can not provide a definitive yes or no for switching a cholesterol lowering agent OTC; they can only provide guidance on how Merck chooses to proceed, but that there is no fundamental opposition within FDA against the switch of a cholesterol lowering agent. FDA stressed that there are fundamental questions that Merck will need to address in future consumer behavior studies and that the results of such studies will determine the fate of the switch.

Question 1: Is the Agency open to using total cholesterol for the Mevacor OTC eligibility criteria and treatment to goal?

FDA Response:

The NCEP ATPIII Guidelines use LDL-cholesterol as the basis for determining the need for cholesterol-lowering treatment in the prescription setting. The condition being treated does not change if it is treated in the OTC setting. Thus, the criteria for determining the need for treatment of that condition should not change either.

Discussion:
Merck described in detail how they came up with the new proposal for eligibility criteria based on total cholesterol and HDL-C in women. They described that there were more consumers in the CUSTOM study that knew their total cholesterol than there were consumers that knew their LDL-C. Merck's decision was primarily driven by the Framingham eligibility criteria, which use total cholesterol and HDL. In addition, Merck looked at data from the National Health and Nutrition Examination Survey (NHANES) 1999-2002 and determined that 21.44% of individuals with total cholesterol between 200-240 mg/dL and 6.16% of individuals with total cholesterols > 240 mg/dL fall within a LDL range of 130-170mg/dL with a 5-20% ten year risk. The NHANES data also demonstrated that 47-49% of women 55 years of age or older with a total cholesterol between 200-240 mg/dL have HDL-C > 60mg/dL. For this reason Merck stated that they plan to have a separate label for women containing exclusion criteria for HDL-C values > 60mg/dL.

FDA raised concerns about self-selection to treating lipid disorders based on total cholesterol and not on LDL-C. While the NCEP ATP III guidelines identify patients based on CHD risk categories which consider Total-C over LDL-C, the decision to initiate drug therapy within a particular CHD risk category is still based on LDL-C. Furthermore, LDL-C remains the target of therapy for the proposed patient population. FDA stated that they are not concerned about dropping triglycerides but they are concerned about dropping LDL-C.

Merck stated that the LDL-C would not be totally dropped but would be used to guide treatment decision after someone starts Mevacor OTC. Merck stated that they intend to provide education to the consumer about LDL once the consumer starts treatment. When the consumer has their cholesterol rechecked they will be taught to base their decision to continue treatment on their LDL-C. Merck stated that the key is to first get them in the door using total cholesterol.

FDA raised issue with having consumers obtain an LDL-C after initiating treatment without a baseline LDL-C. Without a baseline LDL-C you can not evaluate the treatment effect and one cannot expect consumers to understand that LDL is a component of Total-C. FDA indicated that this new paradigm appears to be more complex than just having the consumer understand their LDL-C value at the outset. FDA also noted that by changing to total cholesterol between 200 – 240, they will include a greater percentage of consumers at lower cardiovascular risk.

Merck agreed to further consider inclusion of LDL-C as a self-selection criterion.

Question 2: Is the Agency open to eliminating the need for an additional risk factor for Mevacor OTC eligibility criteria for men?

FDA Response:
The criteria used for determining the need for treatment should be consistent with the NCEP ATPIII Guidelines.

Discussion:

This question was addressed with Question 1. No further discussion was generated specific to Question 2.

Question 3: Does FDA find it acceptable for some consumers to want to discuss the product with a healthcare professional before making a purchase or ongoing use decision?

FDA Response:

It is acceptable for consumers to speak with a healthcare professional. The key word here is "some". If "some" means that 75% of the consumers need a healthcare provider to make a decision, it is not clear this is what will happen in the OTC setting If the proper use of the product is primarily driven by having contact with a healthcare professional, we would have concerns about the applicability to someone who does not have a physician. If a study participant does have contact with a healthcare professional, we would like to see documented, as part of the proposed self-selection study:

- *that those consumers who say they want to speak with a healthcare professional actually do*
- *what the healthcare provider advised. [By the design of your study, it does not appear that the study allows a participant to talk to a doctor. If a participant chooses to talk to the doctor, is this a correct self-selection or is this a default response (depends on how you design the study)?]*

Demographics should include whether or not the study participant has a healthcare provider.

We are most interested in the behavior of those study participants who do not have contact with a healthcare professional.

Discussion:

Merck stated that the self-selection study they are proposing does not put "asking the doctor" as a primary focus. Merck explained that the study is designed to see how consumers behave without first interacting with their doctor. Consumers will be asked if they would prefer to speak to their doctor prior to making a use decision and, if this is the case, extensive data will be collected to look at the reasons why.

FDA agreed that obtaining data on why consumers feel they need to talk to a doctor is important. FDA noted that in the CUSTOM study and in the label comprehension study, the "fall back answer" that was considered acceptable was "talk to a doctor". Adequate data

was not collected to understand why. If a large percentage of consumers want to talk to their doctor prior to using the product, we need to understand the reasons. FDA is most interested in those consumers that do not wish to consult with a healthcare professional prior to self-selection and what the resulting purchase decision and usage pattern is.

Merck agreed with FDA's statement and further clarified that the intention of their self-selection study is to see how well consumers can self-select without consulting a healthcare professional.

FDA pointed out that in the proposed study design all consumers will have their cholesterol checked and the information provided to them prior to the self-selection assessment. FDA suggested that Merck should keep the same recruitment paradigm used in the CUSTOM study where consumers were asked to come to the study knowing their cholesterol information. In the new self-selection proposal, cholesterol testing could be provided to a consumer but only if the consumer asks without prompting from site personnel. This will keep the self-selection process more naturalistic.

Merck agreed and stated that they understand that FDA will need to see all the protocol details including the script on what information is presented to the consumer and when.

Question 4: Will the Agency accept some behavior of this nature where a consumer makes an informed decision to use the product while not exactly meeting all label benefit criteria (e.g., age)?

FDA Response:

This will depend on the clinical significance of the behavior. You should analyze consumer motivation to use Mevacor, and test whether they understand the risks and the need to take Mevacor long term in order to achieve benefit. A large amount of data will need to be collected to evaluate behaviors associated with incorrect self-selection. For example, if someone decides to use the product but has very little likelihood of benefit with long term use, it would be important to understand why they decided to use the product given that it would provide little benefit. If it is apparent on further questioning of the subject that they actually did not understand the low likelihood of benefit, then this would not be deemed acceptable. Thus, it is important that the information collected is targeted and does not simply depend on standard questions.

Discussion:

Merck stated that they understood that FDA is not comfortable with consumers choosing to use a product when they don't meet the label criteria. Merck reemphasized that they recognize the need to obtain data on why consumers make incorrect choices, for example, why consumers chose to take a product even if they understand that the label states that they should not use the product.

FDA agreed with Merck's statement emphasizing the need to understand why they did not behave as directed by the label.

Question 5: Does the Agency agree that label comprehension studies and a self-selection study will address the major concerns regarding consumer behavior as expressed in the Action Letter?

FDA Response:

The primary area of concern in the CUSTOM actual use study was the high rate of incorrect self-selection. We would like self-selection improved. We suggest you test multiple versions of the label and select the most effective one. This testing should include a comparator with a label that is in Drug Facts format according to 21 CFR 201.66. Consumers are now accustomed to the Drug Facts format and may have improved comprehension when reading a label in this format.

If the program becomes substantially changed it may not correlate with the actual use data from the CUSTOM study. If the labeling and program are substantially different from what was evaluated in CUSTOM, you will need to provide data on how you plan to correlate the consumer use data from the CUSTOM study with the self-selection data from the self-selection study. The need for an actual use study will be determined by how much you deviate from the labeling and ancillary measures utilized in CUSTOM.

Discussion:

Most of this issues pertaining to this question were addressed in the previous questions.

FDA stressed the need to design a new label in Drug Facts format. Merck stated that they have moved away form their version of the label that does not comply with drug facts format to a label that does comply with drug facts format.

FDA also reminded Merck to be sure to complete their pivotal label comprehension study before doing the self-selection study.

No further discussion was generated in regard to Question 5.

Question 6: Does the Agency agree with or have comments on the basic elements of the proposed study design (e.g. recruitment methods, exposure to in-market advertising, providing a lipid profile test, sample size, no opportunity for checking with a doctor)?

FDA Response:

- *We encourage you to submit a protocol and labels for the Agency review prior to initiation of the study. The proof is in the details and there are not enough details provided.*
- *We have concerns about proactively providing an advertisement to prospective participants prior to making a self-selection decision. Consumers should not be given any advertisement material that provides information on self-selection as described in your research design. This is much different from people simply having access to information at the point of purchase.*
- *You are going to determine whether or not someone would purchase a product as the measure of self-selection. Given that there are many reasons why someone would not purchase a product, we can not assume that people who do not purchase the product made*

a correct self selection decision. There is not enough information provided about how this process will work and warrants further discussion.

- *You have not provided information on the how the sample size was determined.*
- *We need additional information on what a consumer will actually be told prior to participating in the study. If consumers know that they can not purchase the product or leave the store with the product, does this influence the self-selection decision.*

Discussion:

The study should not provide any advertisement other than what would occur in the real world. Using shelf talkers would be acceptable.

Question 7: Will a study of this design and magnitude satisfactorily address the concern about the safety of lovastatin in consumers with undiagnosed liver disease and no baseline liver function testing?

FDA Response:

Yes, subject to review of the data.

Discussion:

Merck stated that they recognize that the final issue on liver function tests can not be determined until the data has been reviewed.

Question 8: Has the FDA evaluated our proposal and determined if this brand name is acceptable?

FDA Response:

According to DMETS (Division of Medication Errors and Technical Support) MEVACOR™DAILY is not acceptable. They recommend not including the dosing regimen in a drug name because of potential changes in dosing regimens that can occur. MEVACOR™ OTC is acceptable.

Discussion:

Merck inquired if there was any flexibility in this decision. Although Merck had used Mevacor OTC as a "placeholder" for a while, they had not intended to use that name commercially. They were still most interested in pursuing the name Mevacor Daily.

FDA stated that Merck can resubmit the name Mevacor™ Daily and it can be re-evaluated. The DMETS evaluation is a recommendation for the review team to consider in its own decision, but that the review team will need to discuss differences of opinion with DMETS if a decision is made not to follow DMETS recommendations.

Question 9: Does the Agency have any additional comments on our response to the marketing issues or any other recommendations which could help us better direct our future work effort?

FDA Response:

Any information that is used to enhance the self-selection process during the self-selection study will need to be considered labeling and would be required in all marketing venues. If any of this informational material were to be removed, data would need to be provided that demonstrates the consumer's ability to correctly self-select without this material.

Discussion:

Merck stated that they understood FDA's response to Question 9. No further discussion was generated.

Closing statements:

Merck closed by inquiring if FDA is committed to work with them as they develop their protocols. Merck also restated their concern about people within the FDA who may continue to have philosophical concern, no matter how impressive the data are, about bringing a cholesterol lowering agent to the OTC market.

FDA stated that there will be people with philosophical concerns, however, there is no monolithic view in FDA that this is a bad idea. If this was the case, Merck would have heard that by now. The closer Merck can get at addressing all the concerns, particularly with the remaining OTC issues, the better off Merck will be in lessening the impact of the philosophical concerns.

FDA reminded Merck to ask for feedback in the cover letter when they submit a protocol for review, if they wish to wait for feedback.

FDA asked Merck to change the pregnancy wording when they develop their new label from "are of childbearing potential" to "can become pregnant". Merck had some concerns about specific wording on the label to make sure that it is reflective of the data concerning pregnancy.

The meeting ended at 3:30 pm.

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/s/

Charles Ganley
5/3/05 02:15:51 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Division of OTC Drug Products
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: July 25, 2005

To: Florence F. Vickers, Ph.D., F.C.P.	**From:** Laura Shay, MS, RN, C-ANP Regulatory Project Manager
Company: MERCK	Division of Over-the-Counter Drug Products
Fax number: 484-344-3682	**Fax number:** (301) 827-2315
Phone number: 484-344-4511	**Phone number:** (301) 827-2274

Subject: Comments of Self Selection Study Proposal

Total no. of pages including cover:

Document to be mailed: ❑ YES ☑ NO

Please refer to your June 15, 2005 General Correspondence submitted under your new drug application NDA 21-213 for Mevacor™ Daily (20 mg lovastatin) tablets.

Below are responses to your questions. If you have any questions you may call Laura Shay, regulatory project manager, at (301) 827-2274.

1. **Does FDA agree with or have comment on the study objectives?**

   We agree with your objectives

2. **Taking into account that this wording will be tested in an upcoming pilot study and may be refined further, does the FDA have any comments or suggestions on language of the self-selection or purchase intent questions?**

- Self-selection Question
  - The self-selection question is currently worded as follows:

    "Thinking about your own medical history and personal characteristics, according to the information described in the label, do you meet all of the requirements on the label, or not?"

The self-selection question should be able to gather the data to meet your study objectives. We recognize that you have tested different ways to pose this question. It is to your benefit to be certain that the low literacy population can comprehend this question so you can gather accurate information in response. We remind you that an adequate number of low literate individuals need to be tested in the self-selection study.

- Purchase Decision Question
  - The purchase decision question is currently worded as follows:

    "Again thinking about your own situation, would you like to put the box back on the shelf, or pay for it now?"

  - If they state they will buy it , they will be asked the following question:

    "After you buy this product, is there anything that you plan to do before you start using it, or not?"

The first purchase decision question appears to be adequate, however we do not anticipate that the second question will yield useful data.

3. **Does the FDA have any comments or questions on the overall study design and sequence of events which we may address before submitting a final detailed protocol for review?**

We have the following comments:

- *Participants can be recruited based on their concern about their cholesterol.*
- *After the self-selection and purchase decision, consumers should be asked to state what they think their own cholesterol values are. This knowledge should be verified by onsite testing.*
- *The call center should not tell the participants the potential price of purchasing the study drug. This could potentially narrow the demographic profile to participants with higher socioeconomic backgrounds.*
- *It is also not naturalistic to alert the study participants a head of time that they should know their cholesterol values and/or bring them to the study site. We agree that it is reasonable to ask participants to fast before coming to the study site because they may need to have a blood test performed.*
- *If participants have not fasted, blood work performed at the time of the visit would be able to address those with low cholesterol. Those with high cholesterol could be asked to fast and return for another blood test.*

There is no guarantee that shelf displays will be consistently available in all marketing venues. Therefore, we recommend the self-selection decision be based solely on the information provided on the outer package. This could include away labels, carton flaps, etc....

Although you did not provide details on your data analysis plan in your self-selection summary, we request that you only provide data for correct and incorrect answers. Provide the number of responses in addition to percentages. We are not interested in considering "acceptable" answers.

It is unclear why you are developing categories for your qualitative data based on previous studies, when new categories may emerge during your self-selection study. A separate categorical review of the data should be performed for the self-section study.

One final comment regarding the label you sent for review on May 20, 2005, we recommend that you add and test consumer understanding of grapefruit juice as a contraindication. In order to remain consistent with prescription labeling, the Drug Facts Label should include the warning that Mevacor should not be taken with: "Large quantities of grapefruit juice (>1 quart daily)."

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/s/

Laura Shay
7/25/05 11:16:09 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-213

Merck& Co., Inc.
Attention: Florence Vickers, PhD.
Director, Worldwide OTC Regulatory Affairs
Sumneytown Pike, P.O.Box 4, BLX-29
West Point, PA 19486

Dear Dr. Vickers:

This letter is in response to your June 10, 2005 letter requesting a revision to paragraph one on page 4 of the April 25, 2005 meeting minutes. In your letter you request the changes that are underlined below:

Merck described in detail two alternative label paradigms that were developed in an effort to simplify the label evaluated in the CUSTOM trial. One remained an LDL-C based paradigm and the other was based on "total cholesterol. This included a description of how they came up with the new proposal for eligibility criteria based on total cholesterol and HDL-C in women. They described that there were more consumers in the CUSTOM study that knew their total cholesterol than there were consumers that knew their LDL-C. Merck's decision to consider a total cholesterol label paradigm was primarily driven by the Framingham eligibility criteria, which use total cholesterol and HDL. Merck presented data from the National Health and Nutrition Examination Survey (NHANES) 1999-2002 *which they felt demonstrated that* the distribution of CHD risk in those eligible for either of the two alternative labels was very similar to that targeted by the CUSTOM label. *Merck also presented that* the NHANES data demonstrated that 47-49% of women 55 years of age or older with a total cholesterol between 200-240 mg/dL have HDL-C> 60mg/dL. For this reason Merck stated that they plan to have a separate section in the label for women containing exclusion criteria for HDL-C values> 60mg/dL.

We agree with the above paragraph with minor edits written in italic and will consider this revised paragraph part of the official meeting minutes.

If you have any questions, call Laura Shay at (301) 827-2274.

Sincerely,

{See appended electronic signature page}

Laura Shay, R.N., M.S., C-ANP.
Regulatory Project Manager
Office of Nonprescription Products, HFD-560
Center for Drug Evaluation and Research

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/s/

Curtis Rosebraugh
8/2/05 09:53:30 AM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 7, 2005

TIME: 2:00-3:00 PM

LOCATION: Teleconference

SPONSOR: Merck Research Laboratories (a division of Merck & Co., Inc.)
Johnson & Johnson Merck Consumer Pharmaceuticals Co. (JJMCPC)

TYPE OF MEETING: Type C, Advice

DRUG: Mevacor™ Daily (20 mg lovastatin) tablets

APPLICATION: NDA 21-213

MEETING CHAIR: Andrea Leonard-Segal, M.D., Acting Division Director

MEETING RECORDER: Laura Shay, Regulatory Project Manager

FDA ATTENDEES:

Division of Nonprescription Clinical Evaluation:

Andrea Leonard-Segal, MD, Acting Director
Daiva Shetty, MD, Medical Officer
Michael Koenig, PhD, Interdisciplinary Scientist
Leah Christl, PhD, Acting Chief, Project Management Staff
Laura Shay, RN, MS, Regulatory Project Manager
Susanna Weiss, PhD, JD, Social Science Analyst
Stan Lin, PhD, Statistician

EXTERNAL CONSTITUENT ATTENDEES:

Merck Research Laboratories (a division of Merck & Co., Inc.)
Johnson & Johnson Merck Consumer Pharmaceuticals Co. (JJMCPC)

Edwin L. Hemwall, PhD, VP, Global Regulatory & Scientific Affairs, JJMCPC
Jerry Hansen, RPh, VP, Marketing, Rx-to-OTC Switch Business, JJMCPC
Peggy Hwang, PhD, Biometrician, Clinical Biostatistics, MRL
John D. Irvin, MD, PhD Sr., VP, Global Research & Development, JJMCPC
Jeffrey G. Levine, MD Sr., Director, Clinical Research, MRL
Stephanie J. Levy, MA, MBA, Director, Consumer Market Research, JJMCPC
Brenda McGuire, RN, MS, Assoc. Director, OTC Regulatory Affairs, MRL

Paulette Midgette, MS, Manager, OTC Regulatory Affairs, MRL
Amy Replogle, BS, Medical Program Coordinator, Clinical Research, MRL
Robert W. Tipping, MS, Director, Clinical Biostatistics, MRL
Theodore C. Vassil, MS Sr., Clinical Associate, OTC Clinical Research, MRL

BACKGROUND:

Merck & Co., Inc. (Merck) submitted a new drug application (NDA 21-213) on December 10, 1999 for over-the-counter marketing of Mevacor™ Daily (10 mg lovastatin) tablets. A "Not Approvable" letter was sent to Merck on October 6, 2000. Merck joined with Johnson and Johnson forming Johnson & Johnson Merck Consumer Pharmaceuticals Co. (JJMCPC) and resubmitted the application for the marketing of Mevacor™ Daily (20 mg lovastatin) Tablets on August 24, 2004. A "Not Approvable" letter was sent to JJMCPC on February 23, 2005. JJMCPC continues to work on their program in support of this NDA.

On September 22, 2005, JJMCPC requested a meeting with the Division of Nonprescription Clinical Evaluation to discuss their ongoing clinical development program. As stated in the September 22, 2005 Meeting Package, JJMCPC proposes the testing of two different labels (one label using a LDL paradigm and the other label using a total cholesterol paradigm) in their self-selection study (Protocol 086) entitled "Self Evaluation of Lovastatin to Enhance Cholesterol Treatment" (SELECT).

MEETING OBJECTIVES:

To discuss questions specific to Johnson & Johnson Merck Consumer Pharmaceuticals Co.'s proposed self-selection study (Protocol 086) entitled "Self Evaluation of Lovastatin to Enhance Cholesterol Treatment" (SELECT).

DISCUSSION:

Draft responses to the questions enclosed in the September 22, 2005 Meeting Package were sent to Johnson & Johnson Merck Consumer Pharmaceuticals Co. (JJMCPC) via e-mail on December 6, 2005. These draft FDA responses are listed below in italics. Following introductions and a brief discussion of the purpose of the meeting, the meeting agenda consisted of further discussion based on the draft responses from the FDA.

Question 1:
J&J-Merck recognizes that FDA has repeatedly advised that an OTC statin labeling paradigm should be based on LDL-cholesterol, in keeping with current NCEP ATP III Guidelines. In contrast, we have also been advised to simplify the label by both FDA and by the joint Advisory Committees in January 2005. We continue to believe that a label paradigm based on Total Cholesterol can be justified as consistent with the risk-based approach of ATP III and may be more readily understood and correctly followed by more consumers (see Section III). We think this question can be addressed, at least in part, by testing the two paradigms in a Self-Selection study as is proposed here. Label Comprehension testing will also be conducted for both labels. **Does FDA have any comments on this approach and agree that useful information to address this question can be gained from the two-cell design of the proposed Self-Selection study?**

FDA Response:

From a label comprehension and self-selection point of view, we have no problem with your testing the two different labels (one based on LDL-cholesterol and one based on total cholesterol).

The self-selectors in your study should conform to the NCEP ATP III guidelines. We have concerns that the use of total cholesterol and age as self-selection criteria may not capture the same population of users as self-selection criteria based on the ATP III guidelines. If self-selection patterns with the two labels are comparable and you choose to move forward with total cholesterol-based directions for use, then you will still need to demonstrate that consumers can manage their lipid therapy over time based on the LDL-C criteria recommended in the ATP III guidelines. However the degree to which the information is useful is a review issue.

Question 2:

One of the main goals of the labeling to be used in the SELECT Study is to minimize the proportion of participants in the following populations who choose to purchase:

a) Women < 55 years of age: In CUSTOM, of the 685 women less than 55 years of age who evaluated the product, 23.5% (161/685) elected to use MEVACOR™ Daily. We expect to have approximately 200-210 females less than 55 years old evaluate each of the two label paradigms in SELECT (total 400-420).

b) Women of childbearing potential: Questions on childbearing potential were not asked in CUSTOM and there was no warning on the label. It was assumed that the 55 years age cut-off would minimize purchase by women capable of conceiving a child.

c) People with relatively low risk of CHD (<5% risk over 10 years) not matching label criteria: Risk information was not collected from the Evaluators group in CUSTOM so it is not known how many low risk people made a purchase decision in that study. However, 27.3% (289/1059) of the Users in CUSTOM were considered to be of low risk, most of whom were women.

We plan to enroll at least 1000 participants for each label paradigm, with at least 100 purchasers in each of the two groups**.** Based on what was observed in CUSTOM, **does FDA feel this is a sufficiently sized population to assess the self-selection behavior of these key subgroups?**

FDA Response:

We want to understand why individuals of relatively low CHD risk and women under age 55 years and/or of childbearing potential self-select to use Mevacor. We would like self-selection and purchase decision data presented by individuals in order to evaluate the characteristics of these groups of self-selectors. The predicted error rate for these population subgroups is unknown, so it is difficult to recommend a specific number of subjects for each study group. The only recommendation we can make is to have a large enough sample size to ensure that potential errors will be captured.

Please note that the ATP III guidelines do not apply to individuals with a CHD risk of < 10%. Please use this risk limit in designing your study and planned data analyses.

Question 3:
The participants in this study are asked to review label information in order to respond to a self-assessment question asking if they match the label criteria. In order to answer this question, participants need to consider many factors. The first set of data summaries described in the Data Summarization Plan classifies a person as "not consistent per label" if they are wrong on any one of these factors. In the first set of summaries all errors will be counted equally. However, not all errors are of equal seriousness. The safety/benefit summary will overcome those limitations by summarizing the data according to type of error, rather than by individual participant. Furthermore, errors in safety (absolute contraindications and/or relative contraindications) are generally thought to be of greater concern than errors of benefit (label criteria related to CHD risk). Therefore, we plan to place greater emphasis on safety errors when the data are presented in summary form and discussed in the study report. **Does the FDA agree with this approach and categorization of errors? Are there other approaches or summaries which would be helpful?**

FDA Response:

We want to see self-selection errors presented by individual subjects. Your proposed safety/benefit summary with proposed categorization by error type may be included as additional information. While we agree that errors in safety are of great concern, risk becomes the entire concern for persons who use a drug but are not part of a population shown to benefit from use of the drug.

Question 4: A flow diagram of the questionnaire process is included in the Draft SELECT Protocol provided in Section V. Typically a consumer learns about a product through advertising or noticing it on a retail shelf. A decision to purchase usually occurs after reading labeling and deciding whether or not the product is right for them. This study is designed to mimic this self-selection process which begins with a self-assessment of label criteria and ends with the consumer making a purchase decision. **Does FDA have any comments on the language of the questions and sequence of the steps in the interview?**

FDA Response:

We feel that the question for self-assessment of eligibility is too leading. As currently phrased, the question appears to guide subjects through the decision-making process by telling them what to think about before they answer the question. Asking whether subjects "meet all the requirements on the label or not" prompts them to look at the label in a specific way. This is not naturalistic and does not tell us whether subjects think that the product is appropriate for them to use. We suggest that subjects be asked a simple use question such as: "Based on this label, can you use this product?" or "Is this product appropriate for you to use?"

The interview's sequence of steps is acceptable. We need to review the entire script in order to provide further comment.

Question 5: Section IV provides a summary of how we have addressed FDA's comments in their 25-Jul-2005 feedback on our previous Self-Selection Study design proposal. **Are there any questions or concerns regarding how we have addressed FDA's comments?**

FDA Response:

Yes, we have the following comments:

Question 2, part 1:
A low literate population comprising 12.5% of the overall study population may not adequately sample or represent the low literacy American consumer population. The percentage of low literate Americans exceeds the percentage of the population with an eighth grade education or less.

Question 2, part 2:
There is disagreement about the potential usefulness of subjects answering the question, "After you buy this product, is there anything that you plan to do before you start using it?" We feel that information from this question will be useful only if you plan to document and verify that subjects followed through with their proposed actions (such as talking to their doctor).

Question 3, part 6:
We agree that labeling may include all printed materials that contain information about a product and are in close proximity to the retail shelf. In order for these product-related materials at point-of-purchase to be considered labeling, you need to demonstrate that the materials are necessary for proper product use. It is not clear whether labeling should be physically attached to the product when it is used to make a self-selection decision. This issue remains under review with our General Council.

Question 6: Does FDA have any other comments or concerns related to the proposed SELECT protocol and/or the Data Summarization Plan?

FDA Response:

We would like you to include information in the study analysis about subjects who are "undecided" about whether they can use the product. We feel that it is important to capture purchase information on these subjects. The undecided group needs to have an opportunity to make a purchase decision, and their reasons for purchasing or not purchasing study drug should be documented.

*We have the following comments and suggestions regarding the **Drug Facts** portion of container labeling (both "Total Flap" and "LDL Flap"): There are a few portions of the **Drug Facts** label that do not comply with 21 CFR 201.66. We attempted to identify these areas below. As we have stated before in our communications with you, you will need to provide adequate justification that these deviations from 21 CFR 201.66 are necessary for consumer understanding. You can, for example, provide label comprehension data comparing your proposed label to a label that complies with **Drug Facts** regulations.*

1. *Under the **Use** heading**:***

   *The proposed label includes a hairline, three unbulleted statements, and a table listing criteria for using the drug product. These components of the labeling do not comply with Drugs Facts format or content regulations. These are not indication statements and, therefore, should not be place under the **Use** heading. The unbulleted statements may be more appropriate as bulleted*

*statements under **Warnings**. Regarding the table, **Drug Facts** regulations only allows the use of a tabular format under the **Directions** heading (21 CFR 201.66(d)(9)). One option for complying with the regulations would be to move the table outside the **Drug Facts** box. Another option may be to present the tabular criteria as bulleted text inside the **Drug Facts** box.*

*2. Under the **Warnings** heading**:***

A. *Under the subheading **Ask a doctor before use:***

In accordance with 21 CFR 201.66(d)(7), remove the hyphens separating statements following the first four bullets. Use periods in place of hyphens.

B. *Under the subheading **Ask a doctor or pharmacist before use if you are:***

You may want to add a bulleted statement just below the heading to read, "[bullet] unsure of your cholesterol numbers or have not had a fasting cholesterol test within the last year." You may also want to reorganize the section by moving all of the bulleted statements currently in the proposed labeling under a new bulleted statement that reads, "[bullet] taking any of the following:" The statement, "Certain drugs or foods can cause interactions" should either be moved to follow the bulleted statement "taking any of the following:" or deleted.

C. *Under the subheading **Stop use and ask a doctor if:***

The meaning of the graphic is confusing and does not comply with Drug Facts regulations (21 CFR 201.66(d)(7)). In addition, the font color of text within the Drug Facts box must be all black or one color (21 CFR 201.66(d)(3)).

3. Under the ***Directions** heading:*

You may want to add the word "fasting" to the third bulleted statement, so that the statement reads, "[bullet] get a fasting cholesterol test…"

Additional Discussion:

Johnson & Johnson Merck Consumer Pharmaceuticals Co. (JJMCPC) stated that they would like to go over question 2-5 first, followed by question 1 and 6.

JJMCPC asked what FDA thought about the sample size (question 2). JJMCPC stated that they realize that they cannot predict the make up of the responses from the population that will be recruited into the study; however, based on the results from the CUSTOM study JJMCPC would like to establish a ballpark estimate of an appropriate population size.

FDA responded that it is difficult to recommend the number of subjects that would be needed in order to evaluate an adequate percentage of errors when the error rate for the SELECT study is unknown. FDA stated that what they really want is to understand the reasons why people make the self-assessment mistakes they make

JJMCPC agreed that data on self-assessment and purchase errors by the individual subjects will be provided. JJMCPC added that they intend to focus on errors and do not intend to provide a lot of details on those individuals who self-selected correctly.

JJMCPC discussed the difficulties they have had in coming up with the appropriate self-assessment questions. JJMCPC described the number of focus groups and pilot studies they have conducted over the years evaluating self-selection questions. JJMCPC reported that they found that when a general question was asked, such as "is this product right for you?", they were getting a very general answer. When the question was asked with more detail, they report getting more detailed results such as "Yes, but I need to talk to my doctor". JJMCPC added that they realize it is difficult for FDA to fully assess this question without seeing the entire script. JJMCPC stated that they are preparing a submission that will include the label comprehension study protocol and mock labeling. In addition, they will include the entire script for the SELECT self-selection study, and data to justify the wording for the self-selection question. JJMCPC also stated that they are planning to conduct the label comprehension study prior to initiation of the self-selection study. The sponsor stated that they would provide a series of possible self-selection questions for FDA to consider. FDA responded that they would review this information in JJMCPC's next submission.

JJMCPC inquired about the response to question 5 regarding the size of the low literacy population Upon further discussion, FDA and JJMCPC agreed that the size of the low literacy population as proposed in the submission is adequate.

JJMCPC reported that they feel that is it important to ask all subjects who choose to purchase the product "what they plan to do before they start taking the product." They added that many of the studies they conduct are based on self-reported data. They stated that although they were not intending to verify the information, they still felt it to be very useful.

FDA responded that they have no objection to the sponsor collecting the information. However, FDA is not sure they will find it useful in their review.

JJMCPC reported that they were planning on collecting data on what adjunct material the subjects felt were useful or not useful in their decision making process.

FDA asked if JJMCPC was planning to add separate arms to the SELECT study with and without the adjunct labeling. JJMCPC responded that they were not planning to have separate arms looking at self-selection with and without the adjunct labeling but would consider it.

JJMCPC agreed with FDA's response to question 6 regarding the need to let the undecided subjects make a purchase decision. JJMCPC stated that they plan to give all subjects the opportunity to make a purchase decision. FDA responded that the study schematic in their background package did not provide this information. JJMCPC stated that they would be sure to clarify this issue in their subsequent submissions.

In relation to Question 1, JJMCPC described in detail their reason for testing both a total cholesterol label paradigm and an LDL cholesterol label paradigm. It is JJMCPC's belief that most of the subjects will fall within the ATP-III guidelines based on the results from the

AFCAPS/TexCAPS study subanalysis. They further described a discussion that took place during the AC meeting regarding a cost-benefit analysis in that a reduction in cost in the OTC market would increase availability of the medication to a broader population that needs it according to the ATP-III guidelines. JJMCPC also stated that the AC members felt that the proposed population was the correct targeted population with a vote of 24 to nothing. JJMCPC feels that the total cholesterol label will provide an adequate surrogate for the LDL label paradigm according to ATP-III guidelines.

FDA stated that they continue to have concerns about treating the population that is below the 10% ten year risk for coronary heart disease CHD. If there is little benefit to treating this population, then the risk/benefit ratio of lovastatin becomes less favorable. FDA added that this becomes a review issue: what percentage of people at low risk would use this product, and who these people are?

FDA asked JJMCPC how they intended to treat to goal using a total cholesterol paradigm when treatment to goal is based on the LDL. JJMCPC responded that they will provide data to show that total cholesterol is a good surrogate for LDL. They also stated that they intend to use total cholesterol of <200 mg/dL as the treatment goal.

JJMCPC stated that they agreed with all the label comments provided in response to question 6.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Andrea Segal

12/21/2005 02:03:21 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-213

Merck & Co., Inc
Attention: Edwin L. Hemwall, Ph.D.
Vice President, Global Regulatory & Scientific Affairs
Sumneytown Pike, P.O. Box 4, BLX-29
West Point, PA 19486

Dear Dr. Hemwall:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mevacor™ Daily (20 mg lovastatin) tablets.

This letter is in response to your February 9, 2006 meeting request.

We have reviewed the information contained in your meeting package sent to us on February 9, 2006 and have the following comments and recommendations:

Label Development

Question 1.
Does FDA have any comments on the questionnaire revisions, particularly the scenario response choices?

FDA Response:
One of the main goals of a label comprehension study is to see if the respondents miss or ignore the information in the label, and if they superimpose their own personal beliefs and health histories over the labeling information and instructions. The interview script, questionnaire and scenario response choices present several concerns, predominantly related to prompting and leading the study subjects toward particular responses. Several examples are listed below.

a. Page 28, #4:
I would like you to read all of the information on this package. I'm going to leave you alone while you read the information on the package so you have time to concentrate. When I come back, I will ask you some questions about the product. You will be able to look at the package to answer my questions. I will check back in a while to see how you are doing. You will have as much time as you need to read the package. Please make sure to look over the entire package, including the information that is under the flap. (HAND RESPONDENT PACKAGE AND LEAVE AREA SO YOU ARE OUT OF SIGHT OF RESPONDENT)

The underlined text above is not appropriate in that it prompts the study participants to "read all of the information" and "make sure to look over the entire package, including information under the flap." The packaging and the labeling should speak for themselves, just as they would need to do in natural consumer environments such as stores and homes. In real-life situations, OTC

consumers may not look over the entire package or read all the information on the package labeling.

b. Page 29 #6 (and also see bottom of page 30):
This package has a lot of information on it, so for the remainder of the interview, you might find it helpful to look at the package to help answer my questions. Now, I'm going to ask you some specific questions about this product. This is not a test of you. It is a way for us to see how well this package communicates product information. So, again, I want to suggest that you refer to the package before you give your answers. Do not try to answer from memory. Base your answers only on the information provided on the package and not your personal beliefs.

Again, by repeatedly reminding the study participants to "look at the package," "refer to the package before you give your answers," and to "[b]ase your answers only on the information provided on the package and not on your personal beliefs," sets up an unrealistic bias for the study's results. As mentioned above, consumers may not read the packaging and labeling carefully, and they do bring their own interpretations and personal beliefs to bear on their assimilation of labeling instructions. It is important to know exactly when, where, and how the study participants are doing this in relation to the specific information being tested in the label. Only by understanding when and how often this *may be* happening can the label be revised to try to give greater prominence and emphasis to the portions of the label that are being overlooked or over-ridden.

c. Page 30 – True/False/Don't Know Answer Choices:
Subjects have a 1 in 3 chance of guessing the correct answer to several questions (T/F/Don't know, other limited multiple choice questions). Additionally, some of the scenario response choices are extremely leading and virtually give the correct answer away. For example:
"THIS PERSON DOES NOT MEET ALL THE REQUIREMENTS ON THE LABEL AND SHOULD NOT USE THE PRODUCT WITHOUT TALKING TO A DOCTOR."

d. Page 30 ,#20 at the bottom of the page 20:
We're going to look at a few descriptions of different people who are deciding if MEVACOR™ Daily is right for them. I want you to look over the information on each card then tell me the answer on this card that applies to the person being described. (HAND CARD E AND REVIEW ANSWER CHOICES) Remember, your answers should be based only on the information from the package and not based on your own opinions or your own health information. Please remember that you can refer back to the package.

Again, the underlined text above is prompting and leads the study participants with repeated reminders to look at the package label and to base their answers on the package labeling not on personal opinions and health information.

e. Pages 31-32 ,#201-204 and #301-304:
Limitations of forced-choice answers and the wording of the questions give too much information and could be leading. In addition, answer choices limited to three options give the respondent a 1-in-3 chance of guessing the correct answer. Also, the scenario response choices provide too much information and are, therefore, leading.

f. Page 33-35 #22, # 23
As stated above, limitations of forced-choice answers and the wording of the questions give too much information and could be leading.

In addition, the text **"Be aware in some cases, information relating to specific medicines or healthcare products may not be on the package"** is leading in that it tells respondents ahead of the questioning that certain types of information may not be on the package. Through the use of open ended questions, it would be better to wait and see if the respondent tells the interviewer that "there is nothing in the label about Jerry's antifungal medicine" or "there is nothing in the label about John's constipation."

g. Page 36 , #27
Looking at the package, and considering the directions for using the product, how many times a day should someone take MEVACOR™ Daily?

_____(# OF TIMES – NO RANGES)

Y( ) DON'T KNOW

It is leading to steer the respondents to the section of the label concerning "directions for using the product" in order to find the answer to the question "how many times a day should someone take Mevacor Daily?" You need to determine if the label portrays the instruction with sufficient prominence and clarity for the reader to be able to locate the information him/herself.

Also, the interviewer's answer option should not restrict the response to "# OF TIMES – NO RANGES". If a range is given by a respondent, e.g., "1 to 2 times a day," it should be recorded and not altered to fit the desired answer.

h. Page 36 ,#31, 32, 33, and 34
We recommend that you change #31 to an open ended question.

Question #33 contains two questions making it confusing.

We recommend that question 34 be open ended.

i. Page 38 – #501-504 and 601-602
We recommend that you change the following questions to open-ended questions. For example:

j. Page 39 #38c and #701-704
(TAKE OUT CARD J AND TAKE OUT CARDS 701-704 AND SHUFFLE.)
38c. Let's talk about a final group of people. I want you to look over the information on each card, and then tell me the answer on this card that applies to the person being described. Remember, your answers should be based only on the information from the package and not based on your own opinions or your own health information. Please remember that you can refer back to the package. (HAND CARD J). For each person, please tell me whether their risk of heart disease is at the <u>right level</u> to use this product, whether they may be at <u>lower</u> risk for heart disease so they need to ask their doctor

before using this product, or whether they are at higher risk for heart disease so they need to ask their doctor before using this product. Here is the first person. (HAND RESPONDENT FIRST CARD. READ MATCHING STATEMENT BELOW). What one answer on this card best describes this person's situation according to the package? (TAKE BACK CARD AND HAND RESPONDENT NEXT CARD. CONTINUE UNTIL ALL CARDS 701-704 HAVE BEEN READ).

It is not appropriate for the interviewer to keep reminding subjects that **"… your answers should be based only on the information from the package."**

Asking participants to determine if they have heart disease at the "right level" could be confusing to consumers. The consumer only needs to understand how a person's risk factors relate to using or not using Mevacor Daily. The goal is to see whether or not subjects know if the product is right for them or if they should consult a doctor when a person's risk of heart disease is either higher or lower than the "right level" for taking Mevacor according to the label criteria. The respondents should not be handed this information in the answer choices. We recommend that you change #701-#704 to open ended questions.

Question 2.
Does the Agency understand our rationale for the proposed sequence for label testing as well as our plans to use the same label in the Pivotal Label Comprehension and SELECT studies? Are there any other comments or suggestions the Agency would like to make regarding label comprehension testing?

FDA Response:
Yes, the Agency understands your rationale for the proposed sequence for label testing as well as your plans to use the same label in the Pivotal Label Comprehension and SELECT studies. However, there are some serious flaws (see response to Question 1) in the scripts and questionnaires you propose to use for the Pre-Select Label Comprehension Study. These issues should be addressed before you proceed to the Pivotal Label Comprehension Study.

Question 3.
Does the Agency have any additional comments regarding the proposed labels?

FDA Response:
We acknowledge the changes made to the proposed labels following our teleconference dated December 5, 2005. We have the following comments regarding the Alpha and Beta labels submitted on February 9, 2006:

Outer Panel of Fold-Out Label

Consumers should be alerted to the importance of trying diet modifications and exercise before using this product. Currently you have this information under ***Other information*** near the end of the Drug Facts label. Your testing should confirm that study participants notice and understand this information. If they do not, the information may need to be placed more prominently on the label.

One of the heart disease factors included in the CUSTOM label and the more recently tested "J" label has been removed from the chart. The statement "HDL 'good' cholesterol 1 – 39 mg/dL" should be added to the Heart Disease Factors section (as well as to ***Directions*****)** on the Alpha label. In the "Heart Disease Factor" section of the chart, consider where might be the best place to list the HDL cholesterol (if it is included) as consumers are already looking at their cholesterol results for the Step 2 question.

High blood pressure and taking a high blood pressure medicine should be listed separately. One is a condition, and one is an action.

If the Alpha and Beta labels do not achieve the desired levels of comprehension in your initial studies, you may wish to consider the following:

As your self-selection decision table is currently formatted, it may create a logistical problem for consumers; they have to make multiple assessments, remember the results of those assessments, and collate them into a final decision about using Mevacor Daily. Some consumers may have an easier time correctly following the self-selection decision pathway if they can resolve one selection criterion at a time. There may be simple ways to modify your current self-selection table to communicate a very clear step-wise decision-making process that leads consumers to specific yes/no decision-making points based on the criteria in the table.

Drug Facts

1. Individual statements under headings or subheadings should be preceded by bullets (21 CFR 201.66(d)(4)). Bulleted statements should neither be capitalized nor end with periods.

2. Under ***Directions***, move the statement "This product is **only** for you if" and accompanying statements so that these are the first statements under ***Directions***. Consumers should read the criteria for using the product *before* reading dosing instructions.

3. Under ***Directions***, it appears that you left a word out of the statement "Talk to a doctor about a prescription cholesterol medicine." Did you intend for the statement to read, "Talk to a doctor about *using* a prescription cholesterol medicine" (italics added for emphasis)?

SELECT Study

Question 4.
Does the Agency have any comments or suggestions on the questionnaire/script wording and flow?

FDA Response:
We have no comments on the flow but we have concerns about the self-selection question itself. Please see the answer to question 5.

Question 5.
Does the Agency have any further comments regarding the Self Assessment question? Are there specific elements of the wording proposed [above] which are particularly objectionable and for which we may seek compromise?

FDA Response:
As previously suggested in our December 7, 2005 meeting, the self-selection question should be simple, straight-forward, and non-leading.

The proposed self-selection question, as currently worded, teaches the consumer how to approach the self-selection decision potentially biasing the decision making. The label alone should convey this information. We understand your rationale for the proposed self-selection question and acknowledge that consumers sometimes make self-selection decisions based on ideas and values that bear little or no resemblance to the label information. However, as you state on page 64 of your submission, "The objective of a self-selection study is to simulate the choices consumers will make when they see the product on the shelf…." When consumers see a product on the shelf, they only have a label to tell them how to approach their decision regarding product use.

The inclusion of the purchase decision questions is not necessary. Purchase decisions may have nothing to do with whether people understand the label or can self-select correctly based on the label. Purchase behavior is driven by many factors, including product price, store promotions, coupons, etc., which are completely unrelated to information in the label. If you choose to include purchase decision questions in your study we suggest that you keep them entirely separate from anything concerning the self-selection/self-assessment decision.

Question 6.
Are there any areas which require clarification or explanation? Does the Agency have any comments or concerns about any of the information or proposals provided in this submission that have not been the subject of the more direct questions listed above?

FDA Response:
No.

If you have any questions, call Laura Shay, Regulatory Project Manager, at 301-796-0994.

Sincerely,

{See appended electronic signature page}

Andrea Leonard Segal, MD
Director
Division of Nonprescription Clinical Evaluation
Office of New Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Andrea Segal

4/17/2006 05:05:31 PM

FOOD AND DRUG ADMINISTRATION

Meeting Date and Time:	April 30, 2007 1:00 – 2:00 p.m.
Meeting Type:	B
Meeting Category:	IND
Meeting Location:	FDA/White Oak 10903 New Hampshire Ave Room 1417 Silver Spring, MD 20993
Application Number:	IND 76,090
Product Name:	MEVACOR™ (20 mg lovastatin) tablets
Received Briefing Package	March 30, 2007
Sponsor Name:	Merck Research Laboratories
Meeting Requestor:	Brenda McGuire, M.S., R.N. Associate Director Worldwide OTC Regulatory Affairs
Meeting Chair:	Andrea Leonard-Segal, M.D. Director Division of Nonprescription Clinical Evaluation
Meeting Recorders:	Mary M. Lewis Regulatory Project Manager

FDA Attendees:

Office of Nonprescription Products
Charles J. Ganley, M.D., Director

Division of Nonprescription Clinical Evaluation
Andrea Leonard-Segal, M.D., Director
Joel Schiffenbauer, M.D., Deputy Director

Daiva Shetty, M.D., Medical Team Leader
Linda Hu, M.D., Medical Reviewer
Laura Shay, C.R.N.P., M.S., Social Science Analyst
Leah Christl, Ph.D., Chief, Project Management Staff
Mary M. Lewis, R.N., Regulatory Project Manager

Division of Nonprescription Regulation Development
Matthew Holman, Ph.D., Interdisciplinary Scientist Team Leader
Michael Koenig, Ph.D., Interdisciplinary Scientist Reviewer

Office of Pharmaceutical Science, Office of New Drug Quality Assessment
Shulin Ding, Ph.D, Chemist, Pharmaceutical Assessment Lead

Division of Metabolism and Endocrinology Products
Mary Parks, M.D., Director
Eric Colman, M.D. Deputy Director and Team Leader
Eileen Craig, M.D., Medical Officer
Margaret Simoneau, Regulatory Project Manager

Division of Regulatory Policy II
Michael Bernstein, J.D., Director

Office of Drug Evaluation II
Curtis Rosebraugh, M.D., M.P.H., Deputy Director

External Attendees:

Merck Research Laboratories

Edwin Hemwall, Ph.D.	V.P., Global Regulatory & Scientific Affairs
John Irvin, M.D., Ph.D.	Senior VP, Global Research & Development
Jeffrey Levine, M.D.	Senior Director, Clinical Research
Ingrid Adamsons, M.D., M.P.H.	Senior Director, Clinical Research
Brenda McGuire, M.S., R.N.	Associate Director, OTC Regulatory Affairs
Theodore Vassil, M.S.	Associate Director, Clinical Research
Amy Replogle, B.S.	Medical Program Coordinator, Clinical Research
Jerry Hansen, R.Ph.	V.P., Marketing, Rx-to-OTC Switch Business
Stephanie Levy, M.A., M.B.A.	Director, Consumer Behavior Research
Robert Tipping, M.S.	Director, Clinical Biostatistics
Susan Visscher, RAS-CMC	Senior Regulatory Scientist

1.0 BACKGROUND

The development program for nonprescription lovastatin began in 1996 under the prescription IND 23,907. A separate IND for the nonprescription development was established with the Division of Nonprescription Clinical Evaluation IND 76,090, for administrative purposes. On September 15, 2006 Merck Research Laboratories (Merck) submitted an Investigational New

Drug (IND) application for nonprescription lovastatin 20 mg tablets for the treatment of elevated cholesterol for the primary prevention of coronary heart disease.

On December 10, 1999 Merck submitted a New Drug Application (NDA 21-213) for nonprescription lovastatin 10 mg tablets which received a Not Approvable action on October 6, 2000. On August 24, 2004, Merck provided a complete response to the Not Approvable action letter. The response included an amendment to increase the dose of lovastatin to 20 mg plus data from a label comprehension study and an actual use study [the Consumer Use Study of OTC Mevacor (CUSTOM)]. On February 23, 2005, Merck received a Not Approvable action. In an effort to address the deficiencies cited in the Not Approvable action, Merck developed a self-selection study entitled Self Evaluation of Lovastatin to Enhance Cholesterol Treatment (SELECT). The General Investigational Plan for this study was submitted under IND 76,090.

On September 25, 2006, a Nonprescription Drugs Advisory Committee (NDAC) meeting was held to consider issues related to the analysis and interpretation of consumer behavior studies conducted to support marketing of nonprescription drug products. On October 20, 2006 Merck submitted a general correspondence letter to IND 76,090 stating that they would not predefine criteria for success, as was recommended at the NDAC meeting because of the imminent SELECT study start date and prior agreements between Merck and FDA.

Merck Research Laboratories submitted a meeting request to the FDA on February 23, 2007 to discuss the preliminary results of the SELECT Self-Selection Study; the results of label comprehension studies, and plans for a complete response to the February 23, 2005 Not Approvable letter for NDA 21-213.

2.0 DISCUSSION

Preliminary responses to the questions enclosed in the March 5, 2007 Meeting Package were sent to Merck via email on April 27, 2007.

Following introductions and a brief discussion of the purpose of the meeting, the meeting agenda consisted of further discussion based on the preliminary responses from the FDA. The questions from Merck appear below followed by the preliminary FDA responses in italics. A summary of the discussion during the meeting follows each question. For questions where no additional discussion is indicated, neither Merck nor FDA raised any additional issues pertaining to these questions at the meeting.

Question 1:
Tab C of the Background Package provides an outline of our plans for providing a Complete Response to the deficiencies identified in the February 23, 2005 Not Approvable Letter. Where appropriate, this resubmission will make reference to the original NDA application (December 12, 1999) and the Complete Response to the 10/16/00 Not Approvable Letter (August 24, 2004). The prior submissions were provided in NDA format, but the upcoming resubmission will be in CTD (Common Technical Document) format.

a) Do the plans appear to represent a Complete Response to the February 23, 2005 Not Approvable letter?

FDA Preliminary Response:
Your plan appears to address most of the deficiencies summarized in the NA letter. However, determination of whether the submission represents a Complete Response to the February 23, 2005 Not Approvable Letter is a review issue and will be decided upon resubmission. We also refer you to our response below under part b of this question.

b) If not, what areas may not be adequately addressed?

FDA Preliminary Response:
See our response to question 6 regarding chemistry issues that must be addressed.

Submit the final study report for the Pilot Study of Lovastatin in the KPNC Liver Disease Population, as well as the results of the full KPNC "Study of Potential Hepatotoxicity of Lovastatin in the Northern California Kaiser Permanente Liver Disease Population."

If you propose that the Total Cholesterol paradigm label should be the label for MEVACOR™, provide evidence that demonstrates that the eligibility criteria in that label (for both men and women) target the same CHD risk population as the LDL-C paradigm. Also, provide evidence that consumers using the TC label can appropriately assess their treatment goal which, as per NCEP ATP III guidelines, is based on an LDL-C target.

c) Are there any comments on the overall formatting plan?

FDA Preliminary Response:
No.

Additional Discussion:
Merck stated that they are planning to use LDL as the primary paradigm, but they also plan to collect information on the TC paradigm. Merck stated that they believe that the populations are essentially the same.

FDA raised the following concerns:

- **Would consumers confuse TC and LDL numbers?**
- **Would consumers who self-select according to TC be able to monitor and determine treatment goals based on LDL cholesterol? Additional studies may be needed to evaluate if consumers who self-select based on TC, can identify treatment goals based on LDL cholesterol.**

Merck stated that their program provides education that would inform consumers to evaluate LDL cholesterol levels. However, they are not prepared to do another Actual Use study. Merck also stated that if they choose the TC paradigm, the treatment goal would also be based on TC. They stated that based on the information from previous studies, there would be ways to bridge the data (extrapolation from LDL to TC) .

Question 2:
Merck's response to FDA Comment #8 of the Not Approvable Letter (provided under Tab A) describes our approach to updating the safety information. This includes a proposed plan to summarize post-marketing adverse event data covering the time frame from June 1, 2003 (last submission cutoff date) through December 31, 2006, and literature covering the time frame from April 1, 2004 through December 31, 2006, focusing on key organ systems associated with statin use.

Does the Agency have any comments or questions on our plan to provide updated safety information on lovastatin?

FDA Preliminary Response:
We would like you to do a complete analysis of all adverse events (AEs) and the literature over the dates you have proposed, however, you may focus on the areas discussed on p. A-15 of the meeting package. We request that you summarize and analyze all adverse events and literature, and detail any significant changes in the safety profile since your last submission. Also, we request you provide a table summarizing the submitted articles. If there is a delay in the submission, you may need to update your safety data.

In addition we request that you provide the safety data for the clinical studies that you have conducted since the last submission.

The United Kingdom (UK) government changed the prescription policy of statins, making low-dose simvastatin (10 mg) available as a behind-the-counter drug in August, 2004. We would also like to see any safety information (e.g., concomitant medication use, adverse events related to hepatic or muscle toxicity, drug-drug interactions) on the non-prescription simvastatin 10 mg program in the UK.

Additional Discussion:
Merck stated they have updated the safety database from 1997 to 2003, and they would scan the literature to see if there is further updated safety information.

FDA asked if there was information on the safety profile of Zocor noted after the shift in marketing in the UK to non-prescription, behind-the-counter status. Merck stated that they have ready access to the Zocor data (10 mg simvastatin) data and they will provide that data in the submission. Merck replied that there have been no unexpected safety issues with non-prescription use, but that Zocor use is much lower than expected. Merck stated that Mevacor is not an approved nonprescription product in the UK.

Question 3:
The Background Package includes a summary of preliminary SELECT Self-Selection Study results under Tab D and includes samples of the Participant Profile sheets that will be used to capture all of the medical, behavior and interview response information for the consumers with incorrect self-selection (self-assessment and purchase) decisions. The chart in Tab C also includes our proposals for the provision of study data from SELECT.

a) Does the Agency have any comments or suggestions for our Participant Profile sheets or the proposal to provide study data in the form of SAS datasets?

FDA Preliminary Response:
Please provide the study data in SAS databases with the code manual and an annotated case report form.

The Participant Profile sheets appear to be a good addition to the data presentation and will help supplement the review process. We request that you categorize the responses from all the open-ended questions and submit the findings in a summary table for both the self-assessment decision question and the purchase decision question. We would like to see data on the reasons why participants made decisions not to purchase and why participants thought the product was not appropriate for their use.

We recommend that you provide us with data–matrix of all of the subjects (rows) and their results [correct (1)/incorrect (2)] for all of the self-selection criteria (columns) with a total tabulation for each criterion.

Subject #/Eligibility Criteria	Age F ≥ 55 yr M ≥ 45 yr	LDL-C 130-170	1+ CHD risk factors	LDL-C >170	Liver disease	Diabetes	Etc…
1	1	1	1	2	2	1	.
2	2	1	1	1	2	2	.
3	1	1	1	2	2	2	.

This will help us to gain insight into what criteria accounted for the highest and the lowest percentages of incorrect and correct self-selection.

Additional Discussion:
Merck states that this method of data presentation is all right with them and encouraged FDA to provide them with additional comments about how to best present the data for review. Merck stated that they will provide verbatim responses to questions.

b) Does the Agency have any comments on our approach to reporting the SELECT Study results as summarized in Tab D?

FDA Preliminary Response:
There seems to be an emphasis on the purchase decision. All data obtained from the self-assessment question and the purchase decision question should be submitted with a separate analysis for each.

We would like to see an analysis of whether self-selection and purchase decisions were correct according to ATP III guidelines for each label, including re-analyses of Figures 2 and 3 in section D.

Purchase decisions and self-assessment decisions in subjects with key ineligibilities of interest (p. D-12) should be presented separately for each label, as well as for combined data from the LDL-C and TC paradigms.

c) Are there any suggestions for modifying our approach to facilitate the OPD review and interpretation of SELECT?

FDA Preliminary Response:
It is unclear who OPD is. See our comments above.

Additional Comment:
Merck clarified that "OPD" in their questions is a typographical error and should have been "ONP".

d) We would like to be aligned with OPD reviewers on how the SELECT data should be represented, especially in public presentations. What approach will the FDA take towards summarizing the SELECT data?

FDA Preliminary Response:
We are unable to comment on how we will approach our summarization of the data until we review the complete submission.

Additional Discussion:
Merck stated they would incorporate FDA suggestions noted in response to question 3, into the NDA submission.

Merck explained that the SELECT study would be analyzed in two ways; by Self Assessment and by Purchase Decision. Merck stated they are not emphasizing the purchase decision results, but are focusing on purchase decision when making direct comparisons to CUSTOM data since only purchase decision, and not self-assessment, was assessed in that study.

FDA stated that they were concerned that the label is significantly different from the CUSTOM label and asked for a rationale for why this comparison would be valid.

FDA also suggested that Merck create several hierarchical schemes to analyze the data for key issues that need to be comprehended for effective and safe use of the product. Merck agreed with this approach and stated that one of the key safety issues will be Mevacor's effect on the liver. Merck stated that they have data from a large study where people with liver disease were treated with Mevacor. Merck asked which division will be reviewing these data and what FDA's view on the liver issue is. FDA stated that these data will be reviewed by the Division of Metabolism and Endocrinology Products before drawing conclusions about the hepatic safety issues related to use of Mevacor.

Question 4:
Tab E of the Background Package describes our plans to organize, summarize and interpret the results of the two main label comprehension studies, as well as the ways in which the data will be provided to the Agency. The open-ended verbatim data from the scenarios and other questions will be grouped into classifications of similar responses, and the grouped data will be provided in a data deck format that shows data from the total sample and key subgroups (provided in a pdf file and desk copy if requested). Due to the large volume of verbatim responses for each question from each respondent, we propose to make this information available in an EXCEL spreadsheet.

a) Does the Agency agree to our providing the grouped responses in a pdf file?

FDA Preliminary Response:
You may provide the responses in a pdf file. However, if you do we also request that you submit the data from the label comprehension studies in SAS or a SAS compatible data set with the code manual and annotated case report form.

b) Does the Agency agree to our providing the actual verbatim text of consumer responses in an EXCEL spreadsheet?

FDA Preliminary Response:
Yes, we agree.

c) Does the Agency have any additional comments or questions on our approach to reporting and interpreting the label comprehension results?

FDA Preliminary Responses:
No.

Question 5:
Tab F of the Background Package describes our proposed marketing plans for MEVACOR™ Daily.

a) Does the Agency have any questions, comments or suggestions on these commitments?

FDA Preliminary Response:
We would like to see additional information on your post-approval marketing and surveillance plans. Marketing commitments may be reassuring and may help to allay some concerns as expressed in the NA letter. We will need to further discuss FDA's purview over this type of information.

Our primary interest is in the parts of your program that are essential for achievement of proper self-selection and use by OTC consumers. Ultimately, what is essential is a review issue and must be part of the labeling.

b) Will OPD leadership be willing to endorse these or some modified future version of these plans as responsible, meaningful and generally enforceable?

FDA Preliminary Response:

Your question is hypothetical and based upon the general description of the plans you provided we cannot respond to it at this time. Please see our response to question 5a.

We acknowledge that you are expending effort to design an educational program to support the safe and effective use of MEVACOR™ by OTC consumers and we are open to considering the content of these programs.

Additional Discussion:

Merck raised the possibility of a third class of drugs ("behind the counter") in the United States, which Merck would be willing to consider for Mevacor marketing. FDA could not respond to this issue at the time. Merck stated their willingness to commit to post-approval marketing and surveillance plans, but Merck would like some indication of support from the FDA before presenting their approach to an Advisory Committee meeting. Merck stated their concern that Advisory Committee members would conclude that these commitments could not be enforced and therefore potentially discount these plans.

Question 6:

Additional Discussion:

Question 7:
This NDA has been reviewed twice by the Nonprescription Drug Advisory Committee (NDAC) and the Endocrine & Metabolism Advisory Committee (EMDAC). In January 2005, the key questions regarding safety and efficacy were addressed with strongly positive votes (some unanimous). The remaining questions and the focus of the subsequent Not Approvable Letter centered on the need to improve upon measures of consumer comprehension and behavior, especially self-selection.

Does FDA agree that issues of safety and efficacy of lovastatin 20 mg have been fundamentally resolved and that the focus of a potential third Advisory Committee meeting should be on SELECT results and label comprehension?

FDA Preliminary Response:
Prior to the review of the proposed submission, it is premature to decide that the focus of a potential third Advisory Committee meeting should be limited to the SELECT results and label comprehension.

3.0 ACTION ITEMS

1. Merck will provide the data on Zocor, 10 mg simvastatin, from UK marketing with their submission.
2. Merck will incorporate FDA suggestions with relation to submitting SELECT Self Selection information.
3. FDA will strive for feedback to Merck regarding the status of third-class drugs.
4. FDA will respond to Merck after internal FDA discussion regarding manufacturing lovastatin

4.0 ATTACHMENTS AND HANDOUTS:

There were no attachments or handouts.

5.0 POST-MEETING ADDENDUM:

Upon further discussion with the Office of New Drug Quality Assessment, Division of Nonprescription Clinical Evaluation, and Division of Metabolism and Endocrinology Products,

it is necessary for the prescription NDA (NDA 19-643) to be updated and approved with the new CMC information. However, you can submit the OTC switch NDA (NDA 21-213) with the new CMC information along with a prior-approval supplement to Mevacor prescription NDA. Approval under the prescription NDA will be required as a condition of approval for the OTC NDA.

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/s/

Andrea Segal
5/30/2007 01:36:49 PM