DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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

Volume II

Friday, January 14, 2005

8:00 a.m.

Versailles Ballroom
Holiday Inn
8120 Wisconsin Avenue
Bethesda, Maryland

PARTICIPANTS

Alastair Wood, M.D., Chair
LCDR Hilda Scharen, M.S.,Executive Secretary

MEMBERS OF THE NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

Neal L. 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. (Consumer Representative)
Wayne R. Snodgrass, M.D., Ph.D.
Robert E. Taylor, M.D., Ph.D., FACP, FCP
Mary E. Tinetti, M.D.

MEMBERS OF THE ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

Thomas O. Carpenter, M.D.
Sonia Caprio, M.D.
Dean Follman, Ph.D.
Michael R. McClung, M.D.
Steven W. Ryder, M.D.
  (Nonvoting Industry Representative)
David S. Schade, M.D.
Morris Schambelan, M.D.
Nelson B. Watts, M.D.
Margaret E. Wierman, M.D.
Paul D. Woolf, M.D.

TEMPORARY VOTING MEMBERS
Government Employee:

Susan Makris, Ph.D.

Special Government Employee Consultants:

Richard A. Neill, M.D.
James Schultz (Patient Representative)

PARTICIPANTS (Continued)

FDA

Jonca Bull, M.D
Charles Ganley, M.D.
Robert Meyer, M.D.
David Orloff, M.D.
Mary Parks, M.D.
Curtis Rosebraugh, M.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. WOOD: Let's get started.

LCDR SCHAREN: Good morning. The following announcement addresses the issue of conflict of interest and is made a part of the record to preclude even the appearance of such at this meeting.

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

In accordance with 18 USC 208[b][3], full waivers have been granted to the following participants. Please note that the following consulting and speaking activities waived are unrelated to Mevacor and its competing products: Dr. Michael McClung for consulting for the sponsor and a competitor which he receives less than

$10,001 per year per firm; Dr. Morris Schambelan for consulting with a competitor which he receives less than $10,001 per year; Dr. Paul Woolf for consulting with a competitor which he receives less than $10,001 per year; Dr. Margaret Wierman for being a member of the sponsor's and a competitor's speaker's bureau which she receives between $10,001 and $50,000 per year from the sponsor and less than $10,001 from the competitor; Dr. Nelson Watts for being and advisory board for two competitors for which he receives less than $10,001 per year per firm; Dr. Neal Benowitz for consulting with a competitor which he receives less than $10,001 per year and his spouse's stock in the sponsor which is sponsor which is between $5,001 to $25,000 per year.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

We would also like to note the Dr. Steven Ryder is participating in this meeting as a

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

In the event that discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

Thank you.

Open Public Hearing

DR. WOOD: Let me follow that with this statement. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To

ensure such transparency at the Open Public Hearing Session of the Advisory Committee Meeting, FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Now, we will go to the first speaker. But let me sort of lay out the ground rules first.

Each speaker will have five minutes to speak. We will time you for five minutes and, after five minutes, I will cut off the microphone. So your lips will continue to move but that is all we will hear. So I encourage you to get it done in five minutes and let's get started.

What we would like to do is sort of line up the next speaker to be sitting in the chair behind Dr. McClung. The first speaker will be Laurie Tansman from Mt. Sinai Hospital. The next one will be James McKenney.

James McKenney? All right. The speaker after that will be Suzanne Hughes.

DR. McKENNEY: Good morning, members of the FDA, members of the advisory committee, it is my pleasure to be here this morning. I am Dr. Jim McKenney representing the National Lipid Association.

My disclosures are as you see; speaker honoraria from a number of pharmaceutical companies, research grants from many, consulting fees from some, no honoraria or other moneys from

J&J/Merck, Bristol-Myers-Squibb. The National Lipid Association has received educational grants unrestricted from all of these organizations including J&J/Merck and Bristol-Myers-Squibb.

The National Lipid Association is made up of the leading experts and thought leaders in our profession in the area of lipids. People who are in the trenches seeing patients every day, physicians, cardiologists, preventive cardiologists, endocrinologists, internists, family physicians, pharmacists, nurses and dieticians.

Our principal mission is education. We hold regional meetings throughout the year and concentrate on exchange of information and supporting each other. We also are interested in issues that affect us and our patients.

As you know, we deal almost every day with nonprescription medications as we try to manage our patients of which we know little about the efficacy or safety of the manufacturing quality but we know that they are widely promoted with significant claims of efficacy.

As we looked at this issue about a year ago and talked to our members, the line of reasoning went something like this. What do you

think about an over-the-counter statin? The question would be how could they possibly do for the consumer what I do every day. It is much too complex.

But, as we thought further, it is clear, millions of Americans, more than half at moderate to high risk, are not yet receiving treatment after many years now at this. We are not getting the job done. So what do we do? We do more and better educational programs, more and better drugs, more and better screenings, more and better public programs. How do we overcome this issue?

Well, we maybe should consider it. Maybe it is a good idea to give consumers the opportunity to be more involved in their own healthcare and some tools to do that. So we concluded that the key questions around the issue, as you said yesterday, are the inherent safety and efficacy of the product and the efficacy and safety of the

consumer who is trying to carry out that.

So the National Lipid Association went about trying to find evidence. We felt like we should be debating this issue on the evidence and we did that. We conducted surveys of consumers, physicians and pharmacists. We scoured the literature. We found as many consumer-use studies involving statins and we could, more than you have, actually looked at, and would suggest that there are some additional studies you should look at.

NLA, per se, did not take a position on this but yet tried to foster an informed discussion. We have summarized our findings in a monograph which we have supplied to you and there are copies available to the public outside.

We brought this information to four advisory boards and three town halls the most recent of which was at the American Heart Association this past November. Many hundreds of people participated in that.

I want to present to you very briefly some, just a snippet, of some of the information

that we discussed and talked about. This came from our survey of consumers where we found many people are interested in this topic but, interestingly, among those patients who said that they were likely to purchase this product compared to those who were less likely to purchase this product, there was no difference demographically but a remarkable difference in terms of their personal activity about their own healthcare, their pursuit of diet and exercise and the like. So it looks like there is an activated consumer who is interested in this sort of thing.

We were also comforted by their statements that they would stay in touch with their physicians, both before and during and after making this purchase.

In terms of consumer use, per se, these are the studies that we looked at. PREDICT and OPTIONS were actually presented to this committee in 2000 at a part of the petition from Bristol-Myers-Squibb and, of course, CUSTOM, you heard about yesterday.

Here are some of the findings from those three studies. The consistency is remarkable here. Consulting physicians, exercise, and so forth.

I want to share with you, as my green light has come on here, the negative side of things that raise concerns and then, finally, here is the polling data we--[microphone off.]

DR. WOOD: Thank you very much.

The next speaker is Suzanne Hughes and the speaker following that is Stewart Levy.

MS. HUGHES. Good morning and thank you so much for the opportunity to address the committee. My personal disclosures are as follows: I have received speaking and consulting honoraria from AstraZeneca, Bristol-Myers-Squibb, J&J/Merck, Guidant Corporation and Pfizer. My expenses related to my travel for this meeting are paid for by the Preventive Cardiovascular Nurses Association.

Our group is supported by membership dues and funding from multiple members of the pharmaceutical, medical-device and food industries.

We have not received any funding from the sponsor.

PC&A is a national organization of 2000 nurses dedicated to the primary and secondary prevention of cardiovascular disease. We achieve our mission through professional and public education and through increasing consumer awareness of the importance of reducing CVD risk and through advocacy regarding nurses' role in the care of persons at risk for heart disease and stroke.

The nurses on our board and who authored this statement with me average 30 years experience in cardiovascular nursing. We all remember when care of the acute patient was reactive rather than proactive and when available strategies for the treatment of dislipidemia included only agents that were given three times a day, were poorly tolerated and only modestly reduced cholesterol levels and cardiovascular event rates.

All of us in this room know that the approval of Mevacor, the first HMG COA reductase inhibitor in 1987, effectively revolutionized pharmacologic treatment of dislipidemia. In

numerous well-designed trials over ten years, cholesterol-lowering through the use of statins has been found to be remarkably save and effective. The results of these trials have demonstrated substantial reductions in morbidity and mortality but, of the millions of Americans eligible for treatment with these medicines, only a fraction receive these evidence-based therapies. Many who begin taking these medicines fail to continue therapy over time. Barriers to the initiation of and persistence with treatment are complex and multifactorial. Making a statin available without a prescription is one strategy being explored to close the under-treatment gap. This is an option that may be appropriate for those at moderate risk.

The Board of Directors of PCNA acknowledges the potential public-health benefits of OTC availability of low-dose statins. We support the concept of the switch to OTC status based on the satisfaction of the following. The research should indicate that the population who chooses to use this product is comprised of

appropriate candidates for OTC lipid-lowering therapy. The research should indicate that those who elect to use the product follow the instructions on the label with regard to dosage of frequency.

The research should demonstrate that those who elect to use the product consult with healthcare providers for clinical follow up as needed. The promotion of the product must be accompanied by a responsible marketing campaign targeted to the appropriate population.

In closing, we believe that the OTC availability of a statin is likely to be associated with important public-health benefits. This is more than simply a box on a shelf. This new option would allow Americans to take a more active role in their own health and well being. The associated marketing effort will raise awareness of the importance of the treating dislipidemia as a strategy to reduce overall cardiovascular risk.

We believe that this increased awareness will stimulate important dialogue between the

public and the healthcare community. In response, we should all embrace the opportunity to educate our patients and the public not only with regard to the use of pharmacologic lipid-lowering agents but about the central role of nutrition and physical activity on cardiovascular health.

The Preventive Cardiovascular Nurses Association is committed to participating in this important campaign that has clear potential to save lives.

Thank you so much.

DR. WOOD: Thank you very much and thank you for sticking to time.

The next speaker is Dr. Stewart Levy and Robin Edison will follow that.

MR. LEVY: Good morning. I am Stewart Levy from Impact Health. Our goals today are just to talk a little bit about the industry, the biometric testing industry, and also to give you our position as Impact Health in the industry on the opportunity for over-the-counter cholesterol agents.

Also, we are going to give a little background about the education, about how we reach consumers, the process of how we perform health

assessments, clinical testing and examples of different types of programs at retail.

Our overall mission is to create an experience with the consumer that will drive healthy decisions and what we call the teachable moment which will drive decisions to promote healthy decisions related to products, services and lifestyles.

Impact Health has been around for over 17 years in this industry and we have a number of organizations that utilize our services to support their organizations and to reach consumers including advocacy groups like the American Heart Association, various ad agencies, consumer organizations, employers including the U.S. Government which hires our services such as the U.S. Supreme Court and other organizations within the government, health-promotion companies, food organizations that are becoming very active in

performing cholesterol screening and blood-pressure awareness programs at retail, managed-care organizations such as Blue Cross, Blue Shield plans, over-the-counter companies, pharmaceutical industry and pharmacy chains.

I should also disclose that Impact Health has not contractual relationships with either of the OTC statin companies. We do project work on a case-by-case basis.

As I mentioned, we have been around for over 17 years and we hold very high standards in quality. We have CLIA certification and we actually are licensed as a moderately complex laboratory. So we can actually do field-based lipid screening in many of the states that allow this. We do everything according to HIPPA guidelines. We are not a HIPPA-covered entity but we act as one because we have very valuable laboratory information and biometric values with our consumers.

We have the highest standards of professional liability insurance. We also maintain

a very active quality-assurance program which makes sure that all our policies, productions, practices are necessary to assure that the laboratory results are reliable.

We participate in both mandatory and optional proficiency testing and we train our staff extensively on the clinical relevance of the problems, testing protocols, counseling, OSHA, blood-borne pathogens and HIPPA guidelines.

There are different types of organizations that perform clinical testing, as you may be aware. The industry, itself, is what you would call a cottage industry. There are very few national firms that do what we do but, many times, local hospitals, as some may be talking today, are in the community performing health screening services as a way to promote their hospital and their care in the organizations.

There are also advocacy groups that do this and also temporary nursing staffing firms that do screening programs. Many of the programs are not just one and done. There is an interest in the

industry to continue an ongoing relationship with the consumer to make sure that their health is followed up with physicians, et cetera.

It starts with the consulting and marketing opportunity with the venue, with the sponsor, and then what we will do is perform a validated health risk assessment and a questionnaire which will allow us to gain very important information about medical history, whether they are on other prescription products, whether they have a family history of heart disease, and we will use Framingham risk factors in questionnaires into that assessment.

Then we will perform the clinical testing with technology that you will hear more about today. We will have health education performed and our goal is to drive consumers to a healthcare professional. We are not diagnostic. Let me repeat; our goal is to screen that consumer to promote healthy decisions so that they go to their physician and get onto appropriate therapy or, in this case, speak with their pharmacist.

We follow up with the program with reports to the consumers, individual reports, reports to the sponsors, to the venue. We communicate to both

the participant and the physician and we can perform market research and outcomes measurements.

The process is to do a health assessment, to do testing and to do the education.

I am going to skip over this slide and you will have a handout because it is repetitive. There are some examples of different types of screening programs that are done at retail and with different various groups. Here is an example of one.

I am going to wrap up with our position that there is professional staff to support retailers in the field and also those that will perform consultative--[microphone off.]

DR. WOOD: Thank you very much.

The next speaker is Robin Edison and the speaker following that is Boisey Barnes.

DR. EDISON: Good morning. I will describe our work exploring the question of

lovastatin teratogenicity in humans. You have these materials in the handout.

We examined all case reports from MedWatch and other sources which report exposure to any statin drug in the first trimester of pregnancy. This strategy does not permit causal inferences. I will conclude there are potential safety issues requiring careful study independent of whether lovastatin becomes available OTC.

This overview of the mevalonate pathway which the statins inhibit is familiar to you and indicates the diversity of potential drug targets. Cholesterol is synthesized by the embryo not only for the rapid production of new cell membranes but is probably also used in a concentration-dependent manner to control the activity of patterning molecules that direct morphogenesis, initially in the midline central nervous system.

Here is an overview of our case series. Of the 22 total malformation reports, I will highlight patterns in these seven lovastatin-associated cases. Three of these seven

included midline CNS defects. These numbers are tiny. However, it is interesting that holopresencephaly with a background prevalence of 1 in 16,000 births was reported not only following lovastatin exposure but was also the only malformation reported following cerivastatin exposure.

Holopresencephaly is the classic disorder seen in animals given other inhibitors of cholesterol biosynthesis and is seen in some patients with an inborn error of this pathway. We also saw aqueductal stenosis and a large neural-tube defect following prolonged lovastatin exposure. Not shown, there were also two cases reporting neurologic disorders both including seizures and neurodevelopmental impairment.

The multiple malformation VACTERL association was reported following the 10 milligram per day exposure to lovastatin. This particular case had severe defects throughout the axial skeleton and has a background prevalence of 1 in 500,000 births. Again, of interest, there was a

second case of VACTERL association among the malformation reports following simvastatin exposure.

Considering biological plausibility, only the lipophilic statins generated case reports of malformations although the hydrophilic drug pravastatin generated numerous reports as well, all with "normal" outcome.

Lovastatin concentration in embryonic tissues reportedly averages 25 percent of the maternal plasma concentration and we know that its pharmacokinetic parameters vary at least 10-fold among individuals. With respect to embryonic-tissue susceptibility, the earliest area to undergo rapid expansion is the neuroepithelium which shows the highest expression of HMG COA reductase post gastrulation.

Animal studies using statins have shown malformations primarily in the axial skeleton but also include neural-tube defects, neural-developmental deficits and visceral malformations. Other chemicals that suppress

cholesterol levels have induced all three CNS malformations reported clinically following lovastatin exposure.

In vivo, lovastatin decreases cholesterol levels in the CNS both globally and in specific domains of cell membranes notably depleting membrane sites where folate receptors are localized. VACTERL association is induced in a mouse model by decreasing the pathway activity of the cholesterol-mediated morphogen, sonic hedgehog.

So we have an overlap of human and animal findings in the CNS and two reports each of rare malformations associated with cholesterol or hedgehog downregulation. The apparently small population of statin-exposed births reported by the CDC Registry appears insufficient to presume these reports reflect random events or biased ascertainment. Regarding the question of why there are so few malformation reports, many of the malformations have quite high rates of intrauterine lethality, 99 percent, for holopresencephaly and mostly by Week 8.

It is unfortunate that none of the fetal demise or miscarriage cases were autopsied to rule out associated pathological conditions.

Clinically, most case reports stated the drug was discontinued upon recognition of pregnancy including the two cases of holopresencephaly. Both VACTERL cases had more prolonged exposures during organogenesis.

So these materials may support a teratogenic hypothesis linking first trimester lovastatin exposure with human malformations, particularly of the CNS. Prospective studies are required to adequately assess risk.

Thank you.

DR. WOOD: Thank you.

The next speaker is Boisey Barnes and the speaker after that will be Sidney Wolfe.

DR. BARNES: Thank you for allowing me to make this presentation. I am Dr. Boisey Barnes, a practicing cardiologist in Washington, D.C. and a founding member of the Association of Black Cardiologists. I am speaking on their behalf

today.

Four years ago, the FDA rejected a request for over-the-counter availability of low-dose statins. Today, safe and effective use without physician guidance remains a concern. The ABC has given thorough consideration to this issue and does not support OTC availability of statins at this time.

Number one; while low-dose may reduce cholesterol levels, they have not been proven to reduce cardiovascular morbidity and mortality. There are no trials of OTC statins for effectiveness in primary prevention of heart disease. There are no data on compliance with over-the-counter statins.

Number two; there is concern about the people who need high-dose statins might not get them because they would be taking the OTC low-dose statin that was an alternative to seeing the doctor.

Number three; there is less justification of using weaker statins because they do not provide

optimal risk reduction. It appears from recent studies such as PROVEIT that lower LDL is better.

Number four; individuals may lose sight of the need for lifestyle changes if they believe taking a pill will suffice.

Number five; patients who purchase their statins at the local pharmacy or supermarket will miss one of the main messages of prevention cardiology, the importance of global risk assessment. A healthy lifestyle, low-fat diet and exercise may achieve the same results as OTC statins.

Number six; also will pharmacists have the time to determine the individual's risk of coronary heart disease before selling the drug and also giving lifestyle advice.

Number seven; OTC medications are generally for symptomatic conditions. This medication is for an asymptomatic condition. When will we start it? When will we stop it? Examples of this are Prilosec for abdominal pain. You know when you have discomfort. You know when to stop

it. Or Tylenol for knee pain. You know when to start and stop it. This is an asymptomatic condition. Stopping and starting medications can increase your risk for an adverse event.

Number eight; there will be a problem of underdiagnosing and overdiagnosing elevated cholesterol. Elevated cholesterol does not have obvious symptoms and signs.

Number nine; recognition of toxicity which are mainly liver and muscle. I have never a report of a patient dying of liver disease from a statin. However, they may die from serious muscle complications. The risk for muscle complications is increased by coadministration of many medications. The main one is gemfibrozil. From the 3,399 case of rhabdomyolosis that were reviewed extensively from the FDA that were reported, 58 percent of those were given concomitant medication and the number one is that of gemfibrozil. There are other immunosuppressive agents, warfarin, anticoagulants and other medications. The risks increase as you increase age and as you increase

the dose of the medication along with comorbid conditions and renal insufficiency.

Number ten; females. Statins are contraindicated for women who are pregnant or breast-feeding.

DR. WOOD: Thank you very much.

The next speaker will be Sidney Wolfe and then the speaker following that will be Alice Rein.

DR. WOLFE: About four-and-a-half years ago, FDA had a general meeting on the principles that should be adhered to when any drug is being considered for over-the-counter switch. I think that the two most important principles which are relevant here today are: one, ease and possibility of accurate self-diagnosis; two, the benefit:risk ratio and the continued evaluation of it such as continued cholesterol-lowering levels. Related to that is the number of adverse drug reactions or interactions and the ease of detecting them.

If there are numerous adverse reactions or iterations which may not be fully known to the patient or, conversely, to the physician who is not

aware that the patient is also using OTC drugs, there is even more cause for concern.

If any one of these criteria is not met, the decision to switch a drug to OTC is wrong from an overall public-health perspective. If none of the conditions are met, the switch is likely to be an even greater public-health disaster having an overall negative effect on health. For the switch of any statin--in this case, lovastatin--none of the conditions are met and it is virtually certain that more harm than benefit would accrue to such an ill-advised regulatory decision.

Despite the company's efforts to paint the switch as something positive, the analysis by FDA with which I concur seriously undermines any such conclusion.

First, the eased possibility of accurate self-diagnosis. Since the proposed use is primary prevention and people without symptoms, the correct assessment relies entirely on lab tests and the assessment of other risk factors. The data from these studies of label comprehension and from the

actual use of lovastatin yield unacceptable results as far as the ability of very many patients to accurate assess all the factors necessary to qualify as a candidate for this drug.

In terms of the label comprehension, as you have seen in your materials, only 1 percent of the respondents who stated they could use Mevacor OTC right away actually self-selected correctly. In terms of the actual-use study, the current paradigm for the treatment of hypercholesterolemia is individualized based on serum cholesterol and the presence of risk factors.

One of the more disturbing comments I read was that by an FDA reviewer who said the most disturbing results are in self-selection. Over 80 percent of subjects in the study did not self-select appropriately. Only 484 users initially self-selected correctly and I think this is important and, of those, only 68 were able to do this without a physician's input. Sounds like a prescription drug to me.

Nearly one-third of all users had ten-year

risk for CHD of less than 5 percent which is, as you know, a level that does not call for statin therapy.

Benefit:risk ratio and its continued evaluation and adverse drug reactions. The continued evaluation of benefit:risk depends on cholesterol follow up, amongst other things, and many did not have this in this little study. Amongst the average reactions that may be difficult to detect in the absence of physician involvement in a prescription for this drug and, thereby, intervene are asymptomatic elevations of liver enzymes after taking lovastatin or asymptomatic liver disease before using the drug unknown to the patient.

The onset of myositis, muscle inflammation, a possible predecessor for life-threatening rhabdomyolosis, may not alert the patient who is not necessarily under the supervision of a physician and problems can occur.

A recent large case-control study published a month or so ago in Italy also raises

the question of peripheral neuropathy. It is the third such study and they said this is hypothesis-generating, but this is another problem that patient may not link to the drug.

In summary, since, as is the case for a substantial proportion of those choosing to use the OTC version of this drug, their risk for CHD is so low that there is no evidence they will benefit. They are being subjected to the various risks of adverse reactions without any possibility of benefit. Thus, the risks clearly outweigh the benefits for this group.

In addition, it is clear that the availability of easy-to-get OTC statins will deter many from safer, less expensive, preventive measures. Prevention of cardiovascular disease must be a multi-pronged strategy to reduce risk. The use of heavily advertised statins out of the context of medical consultation may impair the development of an integrated long-term strategy for preventing strokes or heart attacks.

Diet and exercise, critically important

components, may be thought to be less important if the primary strategy seems to be a statin drug.

The safety problems, although somewhat rare for statins other than Crestor are especially hard to detect and monitor without physician involvement and, as mentioned above, must be viewed as unacceptable for the large proportion of people who cannot possibly benefit from the drug.

Even for those who might theoretically benefit, for the small fraction that self-select properly, there are serious questions of whether the 20 milligram dose confers any clinical benefit as quoted from, actually, the company.

In summary, we urge the panel, as we did a few years ago, to reject to over-the-counter switch of this drug.

Thank you.

DR. WOOD: Thank you.

The next speaker is Alice Rein and the speaker following that will be Penny Kris-Etherton.

MS. REIN: My name is Alison Rein and I am the Assistant Director of Food and Health Policy at

the National Consumers League. I am here today to present some of the key findings from a research project that we recently conducted to explore consumer awareness of and attitudes about cholesterol and possible treatment options.

My presence at this meeting is independent of the sponsor but approximately 1 percent of NCL's operating budget comes from unrestricted research pharmaceutical grants of which this study was one.

I will begin my comments with a brief overview of NCL. I will then explain our interest in this topic, describe the research methods used and present a top line of our findings. Given the brevity of this presentation, I would ask that you refer to two supplemental documents for more detailed information. One is a full survey instrument with annotated results and the second part is a PowerPoint presentation depicting key findings and graphic representation. Both of these have been submitted for your review.

The National Consumers League, founded in 1899, is a private, nonprofit advocacy group that

uses education, research, investigation, publications and public/private collaboration to accomplish its mission of representing consumer interest on marketplace and workplace issues.

NCL commissioned this research to explore consumers' knowledge about the significance of high cholesterol, their attitudes toward the possibility of an OTC statin, their perceptions about the relative benefits of OTC versus prescription treatments and their perspectives on relevant safety and use issues.

In exploring this topic, NCL is not lending support to the approval of an OTC statin. We look to the FDA to consider all of the clinical and consumer use data and hope only that these consumer survey data will help inform that discussion.

NCL engaged Harris Interactive to conduct this survey with members of the Harris Poll On-Line Panel which consists of several million people who have agreed to participate in survey research projects. Interviews were conducted between August

26th and September 3rd, 2004. A total of 2,777 people participated in the survey, 730 of whom were qualified to complete it.

The sample was composed of U.S. residents, aged 35 or older, who were either at known moderate risk for coronary heart disease or who were at potential moderate risk for coronary heart disease based on specified risk criteria. None of the survey participants were using medical management to treat their cholesterol.

We oversampled black and Hispanic respondents and used demographic and propensity-weighting techniques to ensure that the data represented the national population of adults aged 35 and older. Near the beginning of the survey, respondents were asked to consider a full description of the proposed OTC statin product.

In OTC/prescription comparison sections of the survey, respondents were instructed to consider a similar low-dose cholesterol-lowering medication that is available only by prescription from a doctor.

Here are six of our key findings. First, American adults still require substantial education about elevated cholesterol and its associated

risks. Almost 40 percent of all respondents did not know their cholesterol level and almost 30 percent indicated that they were not concerned about their cholesterol.

Second, there is an interest among consumers in an OTC option for lowering cholesterol. The majority of respondents indicated that they would be at least somewhat likely to seek out more information on the product, 67 percent, discuss the product with a healthcare professional, 69 percent, or use the product, 58 percent.

The majority of respondents, 85 percent, also agreed either strongly or somewhat that the OTC statin option would be preferable to taking a prescription drug to lower cholesterol.

Third, while most people believe at least somewhat in the effectiveness of the OTC statin, there are concerns about safety. The large majority, over 90 percent, believe that OTC product

would be at least somewhat effective but almost half did not think that the OTC statin would be more effective at lowering cholesterol than diet or exercise alone.

Over two-thirds are at least somewhat concerned about the potential side effects of cholesterol-lowering OTC and almost one-third do not think that the benefit of a cholesterol-lowering OTC outweighs the risk.

Fourth, the OTC statin option is most strongly associated with concepts of prevention and control of health. It is less associated with concepts of dependence on caretakers and poor health.

Fifth, compared to a prescription option, the OTC statin is seen as more convenient, more natural, less likely to cause side effects and more appropriate for "someone with my healthcare needs." A prescription option is generally seen as more effective, more reliable, more trustworthy and more suitable for someone in poor health.

Finally, respondents expressed a greater

likelihood to consider taking, recommend to a friend or family member or seek more information about an OTC statin relative to a prescription statin option. There is far more information but I will let you review that separately.

Thank you for considering this information.

DR. WOOD: Thank you very much. Perfect timing. The next speaker is Penny Kris-Etheron and the speaker following her is William Greene.

DR. KRIS-ETHERTON: Thank you and good morning. My name is Penny Kris-Etherton. I am a faculty member in the Department of Nutritional Sciences at Penn State University. With respect to personal financial disclosures related to this meeting, I serve on the Medical Advisory Committee for J&J/Merck. I have paid for all expenses incurred to attend this meeting myself.

As a cardiovascular nutritionist with a very deep commitment to educating dieticians to be effective in dietetic practice, I support approval

of OTC statin drugs. Beyond the potential public-health impact of OTC statin drugs on coronary heart disease morbidity and mortality in the United States, there are other benefits that can be realized.

I am going to address two important benefits today. First, OTC statins can be a useful tool for dietician, nutritionists in practice to help their patients achieve LDL cholesterol treatment goals.

As you can see in this slide, diet has a modest effect on LDL cholesterol compared with statin drugs. This figure shows the relative contribution of diet versus statin drugs in lowering total and LDL cholesterol levels. Even maximum dietary intervention doesn't always lower LDL cholesterol sufficiently in individuals who are at moderate risk for coronary heart disease. For these individuals, OTC statins can facilitate meeting LDL goals. Moreover, achieving a positive treatment outcome greatly enhances the dietician-patient relationship thereby achieving

greater LDL cholesterol with diet.

You can see with this next overhead what is achievable with diet. Moreover, achieving a positive treatment outcome enhances the dietician-patient relationship and good interactions between a patient and dietician than can facilitate behavior changes to achieve significant cholesterol-lowering reductions and many other diet-related health benefits.

So the potential outcomes of OTC statin drugs extend beyond cardiovascular disease with improved lifestyle behaviors including diet and physical activity, risk of other chronic diseases can be decreased. Consequently, OTC statins could have marked public-health impacts.

Secondly, the OTC program could beneficially affect the nutritional inadequacy of the diet. In addition, it may help facilitate meeting dietary and physician activity guidelines. The OTC implementation studies indicate that subjects using OTC statins report improved diet and physical-activity behaviors. Given the many

problems with diet and physical-activity practices in the U.S., a program that facilitates positive lifestyle changes could favorably affect public health and deserves strong consideration for support.

The United States diet is low in Vitamin E, calcium, magnesium, potassium. It is high in saturated fat, cholesterol, low in dietary fiber. Very small changes in dietary practices can facilitate achieving recommended micro- and micronutrient intakes.

For example, inclusion of just one orange a day can meet the RDA for Vitamin C. Inclusion of one serving the dairy products could help achieve calcium and magnesium RDAs and help meet recommendations for potassium. Switching from a higher to a lower-fat protein food could help achieve saturated fat and cholesterol recommendations for heart health. These are just a few of many examples.

In summary, I believe, because of the many substantive benefits of OTC statins, that the FDA

should approve them for use. The likely multiple and beneficial health outcomes could have a marked public-health impact.

Thank you very much for your attention.

DR. WOOD: Thank you very much.

The next speaker is William Greene followed by Steve Zatz.

MR. GREENE: Good morning. I am Bill Greene. I am the Director for Clinical Pharmacy Services for Methodist University Hospital in Memphis Tennessee. I also carry a faculty appointment with the College of Pharmacy with the University of Tennessee. I have served as a speaker for Pfizer, for Merck and for Ortho-McNeill, a subsidiary of J&J.

I presently come as a representative of the Executive Committee of the Section of Clinical Specialists and Scientists for the American Society of Health System Pharmacists.

ASHP is the 30,000-member national professional and scientific association that represents pharmacists and pharmacy technicians who

practice in hospital inpatient ambulatory clinics home-care and long-term-care settings. I am pleased to provide the perspective of ASHP on the proposed switch of lovastatin from prescription to over-the-counter status.

ASHP believes that existing models for OTC dispensing do not provide the safeguards required to ensure the safe and effective use of statins as part of a multi-modal approach to preventing coronary heart disease. ASHP does support the goal of extended consumer access to important medications including statins. We encourage consideration, therefore, of alternative nonprescription dispensing models for statin that would advance coronary-heart-disease prevention, provide ready access to assessment and advice from a pharmacist and make the drug readily available through pharmacies.

ASHP has recommended that evaluation and treatment of lipid disorders be guided by the recommendations of the National Cholesterol Education Panel, the latest of which are contained

in the Adult Treatment Panel III Guidelines. Statins are certainly considered the drug of choice for most patients with dislipidemia who require lipid-lowering therapy. They are effective at lowering LDL-C. They reduce events in patients at risk and they reduce mortality in patients with proven coronary heart disease. Clearly, there are benefits of these drugs.

The effectiveness of these drugs in reducing LDL-cholesterol has prompted calls for the reclassification of statins as an OTC medication. Although ASHP does not support reclassification to OTC status as that status is currently constructed, alternative nonprescription models for dispensing these valuable medications should be explored.

To achieve the goal of safe and effective use, any nonprescription-dispensing model for statins should include or should identify candidates based on an assessment of multiple risk factors and other events related to the patient. This process should develop an optimal treatment plan consistent with ATP 3 Guidelines. This

process should allow patients and healthcare providers to monitor the response to treatment including adverse reactions. Finally, this process should maximize the effectiveness of treatment by encouraging adherence and appropriate interactions with other healthcare professionals.

High-risk patients should be able to be triaged for further evaluation. If statins are appropriate therapeutic options, they should be part of a multimodal approach to reducing overall coronary-heart-disease risk. One study has examined the use of statins in a simulated OTC statin. The CUSTOM study provides interesting information regarding the potential of patients to adhere with an OTC process. However, a number of adverse events were noted even in that study.

Caution should be exercised when extrapolating such information to larger population, especially information regarding safety. A system that relies on voluntary reporting of adverse events may be inadequate to protect the public or detect subtle signals.

The existing model for OTC medications would place the entire burden for performing this evaluation and assessment on the patient. Wider

use of drug encouraged by OTC status will result in a broader exposure and in increased risk to patients.

ASHP believes that, for these reasons, reclassification of statins to OTC status as currently constructed is not advisable but that alternative nonprescription models for dispensing these should be explored. Since 1985, the Society has advocated a policy that urges changes in federal statutes and regulations that would create and intermediate category of drug products that do not require a prescription but are available only from pharmacists and other licensed healthcare professionals.

ASHP believes that the regulatory system for this intermediate category should contain the following features; first--[microphone off.]

DR. WOOD: Thank you very much.

The next speaker is Steve Zatz and the

speaker following that will be Bob Dufour.

DR. ZATZ: My name is Steve Zatz. I am the Chief Medical Officer of WebMD. It is a privilege to appear before you today to introduce WebMD and describe our commitment to providing accurate, clear and unbiased health-related information to consumers and healthcare professionals and to improving communications between all parties in healthcare, particularly patients and physicians.

Over the past year, WebMD has been working with J&J/Merck Pharmaceutical Partnership to design educational programs that can raise awareness and educate consumers and providers on the management of mild to moderately elevated cholesterol. WebMD has also worked with J&J and Merck on a variety of programs to educate consumers health professionals on topics unrelated to cholesterol management.

We are here today not to speak for or against allowing Mevacor to be available OTC but to inform the committee members of our capabilities to provide information to and facilitate

communications with patients and healthcare professionals.

According to third-party research, the internet has become the preferred medium for consumers and physicians seeking healthcare information today. WebMD has become the leading and trusted on-line health destination. More than 80 million unique visitors a year view more than 2 billion pages across the WebMD Health Network to research health and wellness information and access our on-line communities and health management tools.

With more than 500,000 physician visits per month, MedScape, our health professional website, has become the leading professional destination on the web designed to meet the substantial and growing information needs of physicians and other healthcare professionals. In 2004, MedScape members completed more than 800,000 CME credit hours making MedScape the leading on-line source on the web for continuing medical education.

WebMD works with many of the country's leading healthcare organizations and government agencies including Health and Human Services, the

Centers for Disease Control, the National Cancer Institute and several state public-health departments to distribute their health information on our websites.

In addition, we publish the official references of the American College of Physicians and the American College of Surgeons. We work with numerous other professional societies including the American Public Health Association, the American Academy of Family Physicians, the American College of Preventive Medicine as well as with foundations such as the Commonwealth Fund and the Markoff Foundation.

With more than 250,000 medical writers, editors and physicians who develop our highly regarded content, WebMD is the website most recommended by physicians to their patients and MedScape is the site most recommended by physicians to their peers. Our mission is to provide timely,

accurate and balanced information that enables patients to make informed decisions about their care and enables physicians to provide care consistent with the latest medical evidence.

In addition, with various health-condition assessment programs and decision support tools, WebMD is in a unique position to provide education and targeted outreach to specific populations. WebMD also provides health-decision support tools and information for large corporate employers and health plans to better enable employees and plan members to take a more active role in their health decisions and to better manage overall healthcare costs.

Today, we provide these employee health tools for many of a largest corporations in the United States. When consumers and physicians need healthcare information, they turn to WebMD. For example, when consumers and health professionals needed up-to-date and unbiased information on the Cox-2 inhibitor class of medications, they turned to WebMD in record numbers. As of December 31,

2004, over 1 million pages of information on the subject had been requested by consumers and health professionals through our websites and e-mail newsletters.

In summary, WebMD is a significant source for health information and we take very seriously or responsibility to be an objective and reliable information resource for Americans. We believe that we can be a vital resource for educating and linking consumers and healthcare professionals regarding appropriate treatment options and stand ready to support your efforts as needed.

Thank you.

DR. WOOD: Thank you.

The next speaker is Bob Dufour. The speaker following that will be Jan Engle.

MR. DUFOUR: Good morning. My name is Bob Dufour. I am the Director of Pharmacy Professional Services and Government Relations for WalMart. WalMart operates pharmacies in Sam's Clubs, Neighborhood Markets, WalMart SuperCenters and WalMart Discount Stores. In the 49 states we

operate, we have 3,500 pharmacies and 10,500 pharmacists on staff. On average, over 100 million customers shop our stores each week.

Prescription statins have improved the health of millions of consumers by lowering their cholesterol levels. If the FDA determines that Mevacor is appropriate as an OTC product, the opportunity to better millions of more lives will be possible.

Historically, products that have moved from Rx to OTC status have increased both the accessibility of the product and the affordability. Consumer awareness of proper cholesterol levels may also heighten with the availability of statins as OTC products.

Preliminary plans have been discussed between WalMart and Johnson & Johnson/Merck in anticipation of the OTC approval. These plans have included, first, testing in a limited number stores a Heart Health section which would make consumers more aware of the testing kits and other health products available. This section, if successful,

could be implemented in more stores as demand for OTC statins increase. Secondly, broadcasting a continuing-education program available to all of our pharmacists via our satellite network.

The objectives of this program include; A, recall of the important concepts regarding lipid metabolism and pharmacology of statins; B, list cholesterol goals for American adults and discuss the treatment gap between those goals and current reality; C, discuss the clinical evidence that supports the move toward broader access and treatment with statin medications; D, identify the types of people who would benefit from access to nonprescription statin medications; E, describe how pharmacists might best interact with self-treating patients to ensure optimal outcomes from nonprescription statin therapy.

Our third initiative would be support from Johnson & Johnson/Merck at WalMart Health Fairs to increase the awareness of consumers and their cholesterol levels. This support would include funding for consumers to have their cholesterol

tested as well as information about proper cholesterol levels.

Fourth, WalMart and Johnson & Johnson/Merck will further discuss the use of other WalMart vehicles to increase awareness after the launch including WalMart t.v., radio, pharmacy bag programs, displays and in-store demonstrations and information programs.

WalMart has provided input to Johnson & Johnson/Merck on consumer-friendly packaging. Our emphasis has been on the patients knowing when and when not to take an OTC statin. Johnson & Johnson/Merck has included warnings for consumers when Mevacor is not appropriate and a four-step process for consumers to determine if Mevacor OTC is appropriate.

The American Pharmacists Association has advocated for a pharmacy-care OTC category. WalMart would be able to limit distribution from our warehouses to pharmacies if the FDA determines this category is necessary. WalMart Pharmacy recognizes the significance of the decision FDA is

considering. If the FDA decides that Mevacor would be appropriate as an OTC product, millions of consumers who are at moderate risk for coronary heart disease would have Mevacor OTC available as an affordable option.

I appreciate the opportunity to be heard today. WalMart Pharmacy is committed to providing affordable healthcare to our consumers and our associates. Thank you.

DR. WOOD: Thank you very much.

The next speaker is Jan Engle and that will be followed by Christopher Maus.

DR. ENGLE: Good morning. Thank you for the opportunity to present the views of the American Pharmacists Association. My name is Jan Engle. I am Associate Dean for Academic Affairs and Clinical Professor of Pharmacy Practice at the University of Illinois at Chicago. I am a former President of APHA.

In the interest of full disclosure, APHA did not receive funding to participate in today's meeting and the views I am presenting are solely

those of the Association and its membership. APHA represents more than 52,000 pharmacists, scientists and student pharmacists in all practice settings.

It is our understanding that the product sponsor's application includes a recommendation that lovastatin, if approved as a nonprescription drug, be distributed only in outlets with a pharmacy.

Over the years, APHA has examined this issue several times and, in August of 2004, we convened a task force to make recommendations for the profession's adoption of a pharmacy-care OTC. So what is a pharmacy-care OTC? Pharmacy-care OTCs are a category of nonprescription medicines available in pharmacies on the open shelf with other over-the-counter medications.

What is different? With pharmacy-care OTCs is the availability of the pharmacist and the marketing of the product, where that product is placed and the pharmacist's preparation to support consumer-pharmacist interaction. Pharmacist intervention is not required but it is strongly

supported for pharmacy-care OTCs for those medications being used for chronic, asymptomatic conditions or other conditions where consumers would benefit from additional interaction with the pharmacist.

The task force developed guiding principles for implementing this new category. Our recommendations address areas such as selection of the product as a pharmacy-care OTC, supporting consumer-pharmacist interaction, the scope of consumer-pharmacist interaction and other relevant services available at the pharmacy.

To support consumer-pharmacist interaction, pharmacy-care OTC products should be carefully placed within the outlet to facilitate direct access to the pharmacist. Promotion of these products should direct consumers with questions to their pharmacist and outlets that remain open when a pharmacist is not on duty, such as a grocery store, for example, should provide alternative methods to counseling such as the telephone, the internet or even appointments with

the pharmacist and this would help facilitate this interaction in a busy practice environment.

In outlets where the pharmacy is only component of the facility, appropriate non-pharmacy staff should also be educated about pharmacy-care OTC products. Staff can direct consumers to the pharmacy area and advise them of the pharmacist's availability for consultation.

In terms of interaction between the consumer and pharmacist, pharmacists can help identify consumers who should use the medication through screening methods, identify consumers who should be referred to other healthcare professionals and also provide appropriate support including lifestyle recommendations.

For pharmacy-care OTCs used for chronic conditions, the pharmacist can provide ongoing support such as monitoring for compliance and therapeutic endpoints. To prepare pharmacists to deliver these services, the task force recommends that pharmacists be educated and trained about these pharmacy-care OTCs, the appropriate patient

population that should use these products, the product risks, what the appropriate monitoring and follow up should be, and also procedures for referring consumers.

Other relevant services should also be available at pharmacies that distribute pharmacy-care OTCs. The task force recommends that outlets provide support services such as point-of-care testing when necessary to identify appropriate consumers and monitor their progress. When such services are not available in the pharmacy facility, referral information should be provided.

Consumers should also be encouraged to report the use of these pharmacy-care OTCs to their pharmacist and their physician. The task force recommends that pharmacists add these products to the consumer's medication profile. Documentation of pharmacy-care OTCs will help pharmacists identify drug interactions, protect against drug-disease contraindications and monitor for outcomes.

To conclude, an OTC designated as a pharmacy-care OTC can provide significant benefit to our consumers. The pharmacy-care OTC approach

would not only provide consumers with greater access to important medications that can benefit their health but would also ensure that consumers have access to the medication expertise of pharmacists to help them use those medications appropriately.

Thank you for the opportunity to present the views of the nation's pharmacists.

DR. WOOD: Thank you very much.

The next speaker is Christopher Maus and he will be followed by Laurie Tansman.

MR. MAUS: Thank you so much for having me today and giving me this opportunity to speak. I am Christopher Maus, CEO of Lifestream Technologies. We are not here to sway the board one way or the other as to the efficacy and safety of Mevacor going over the counter. However, the support of technologies that are now available to facilitate the NCEP Guidelines, many may not be

aware of.

Right now, consumer testing is becoming more and more prevalent throughout those people that are what we call focused on health management. With over 100,000 cholesterol monitors now being used in the consumer market and millions of tests being performed, we see the health guidance to consumers out there taking more control of their own personal healthcare.

Our surveys, we showed that people that purchased these home-testing devices, that 90 percent of them had seen physicians within 12 months. Of that, only 25 percent of the people were actually on therapeutic interventions, drug therapies. 79 percent selected dietary, exercise and other therapies to facilitate their goals and objectives.

One way or the other, the probability is that 80 percent of the people are going to self-treat. If self-treatment is inevitable, then technology is crucial to support this and self-management is an important component.

Physicians, pharmacists, consumers will see point-of-care testing as a critical role.

There are basically three types of testing; screening, the purpose of screening which is identifying people at risk; clinical diagnostics which is used by physicians for the purpose of carrying out the treatment of medicine; and monitoring, long-term support which actually supports long-term compliance to the outcomes.

The NCEP now recommends home monitoring and the NCEP 3 Guidelines recommends home monitoring as good way of increasing compliance which is the biggest issue that confronts all therapeutic intervention for cholesterol lowering since compliance is so low.

Total cholesterol is also identified as good surrogate for LDL which we think is also a very critical component for ease of use by the consumer. Home testing for cardiovascular asymptomatic conditions is not new. It is very familiar to the consumer through blood-pressure testing.

In the market since 1972, there are about 5 million blood-pressure cuffs sold in the United States each year for people taking control of their

own health. Those monitoring blood pressure are very similar to consumers. 80 percent of them are not on drug therapy.

Our product was designed and used by both pharmacists and consumers for both the pre and post of an intervention. One of the product has just been recently approved, cleared, by the FDA that actually does the NCEP Guidelines in the device. So the idea of a questionnaire that you have to fill out to assess the risk factors are no longer limited to just paper in someone's head. We actually give you quantitative outcomes inside that device along with the cholesterol tests.

Along with that, these products are becoming less and less expensive with new technologies that are being introduced that allow you actually to hook directly into the computer utilizing the same strip and seeing the data right on line with the same risk assessments. Not only

do we utilize the risk assessments, we have opportunities to direct the consumer to the physician which we actually do on the risk assessments as submitted to the FDA.

We do body-mass index also telling obesity and amount of overweight. We prompt people to see physicians when required and this is a cost-effective assessment without the assistant of a healthcare professional but has the ability to interact.

Right now, the technology that we introduced was the first ever presented to the FDA that actually allows individuals to store data on memory cards inside devices with the NCEP Guidelines and recommendations in the device which is transferrable. At the physician and pharmacy site, they have the same ability to look at this material and assess it. It can be e-mailed, transferred to healthcare practitioners in the areas that it indicates.

Pharmacy care also can print out actual recommendation problems according to the NCEP.

This is no longer an effort of expressing medical opinion in a non-medical environment but using statistically correct data so you have continuity of message to each and every individual. This can be done at home, with the pharmacist or at the physician's site.

The record-keeping capability and management, the portability, also, is available. We are not saying this is the answer. All we are saying is the technology can support the initiatives by this committee and by people seeking to lower their cholesterol regardless of the method in which they are doing it.

In conclusion, technologies are fulfilling many of the goals and considerations of this hearing and is affordable and convenient at this time with over 25,000 pharmacies--[microphone off.]

DR. WOOD: Thank you very much.

The last speaker that we know of is Laurie Tansman.

MS. TANSMAN: Thank you. Let me just preface my comment by saying my views I am

presenting are solely mine not on behalf of my institution. Let me also say that I am a fan of the statins. They are a remarkable class of drugs and it seems that the positive impact they may have on our health has yet to fully be realized.

But that doesn't qualify it to have OTC status. There are multiple reasons for this but, as a registered dietician, I am going to limit my remarks as they relate to lifestyle changes and I apologize for talking so quickly.

In the same news article that I just cited, Slide No. 2--I am going quickly--Dr. Robert Bonow, past President of the AHA, was quoted regarding is ambivalent feelings about the statins being approved for OTC. There is another problem; human nature. People who ought to be dieting and exercising are going to feel that, since they are taking a pill, they can now continue habits that are unhealthy.

In an article by Gordon, et al., it was written, "However, because of the widespread availability of powerful medications, the value of

therapeutic lifestyle changes, per se, in contemporary medical practice is often discounted by clinicians, health insurers and patients."

This is my first concern. I feel confident that people are going to pay even less attention to lifestyle changes and more readily resort to medication. If they do this, then what about the impact of not making lifestyle changes that are a necessary treatment for other medical problems such as obesity, diabetes and hypertension.

But let's first address the concern about statins going OTC for those having a mild or moderately elevated LDL cholesterol value. Diet therapy is a cornerstone for treatment and is the first treatment in treating such an LDL value. Since it is Merck that is seeking OTC approval for Mevacor, this slide is a direct quote from the 17th Edition of the Merck Manual as it appeared on their website regarding dietary changes in the treatment of mild or moderately elevated LDL cholesterol.

As outlined in this next slide, these are

the guidelines for the therapeutic lifestyle changes diet. What can clinicians do? Well, basically, they can instruct patients to reduce intake of red meat and fried foods, use skimmed milk instead of whole milk, substitute low-fat cheeses for full-fat cheese. But how many general practitioners as well as cardiologists have the time in their schedule to sit with a patient for maybe an hour and review diet records for hidden sources of saturated fats such as the use of coconut milk. This is a staple in food preparation for many ethnic groups.

How many physicians are going to review diet records to develop a useful plan with a patient to help them realize weight loss. If we don't provide the opportunity for a patient to realize appropriate dietary changes, then, of course, the TLC diet may be unsuccessful and medication becomes the only therapeutic option.

This is the real heart of the matter. In a quote from an article by Gordon et al., "Moreover, therapeutic lifestyle changes can

generally be implemented less expensively than most medications and, unlike single drug therapy, favorably affect multiple risk factors."

If we don't provide the opportunity for a person to realize appropriate dietary changes, then, of course, the TLC diet may be unsuccessful and medication becomes the only therapeutic option. This is the real heart of the matter and, in a quote from the article by Gordon that I previously referred to, "The value of therapeutic lifestyle changes, per se, is, indeed, often discounted by health insurers as is evidenced by the lack of insurance reimbursement for nutrition counseling provided by registered dieticians."

This was an issue that I addressed in an abstract I presented at a national conference in 1998. But so much for my first concern. My second concern alluded to earlier is that if people are going to pay even less attention to lifestyle changes and more readily resort to medication, then what about the impact of not making lifestyle changes for obesity, diabetes and hypertension.

This was also identified by Gordon et al. in that same article previously referred to; that is, making lifestyle changes are not only less expensive but favorably affect multiple risk factors.

I am getting ahead of myself. I apologize. I have to back up so I am just going to read this to you. Approval of statins for OTC would mark a major turning point for this drug class and for OTC therapy in general as identified in an article by McKenney. If statins are approved for OTC, then OTC approval for oral antidiabetic agents and antihypertensives cannot be far behind.

This is what I think is really, also, the second heart of the matter and I implore you to really, really, think about the impact an what is going to happen if you approve for OTC statins. This, I really, think is more important than anything else.

Then, just in summary, I just want to say that if we are going to get more aggressive about helping those with mild or moderately elevated LDL

cholesterol--

DR. WOOD: Thank you very much to all the speakers.

Are there any other public comments that we have missed or anyone else that wants to add to the public record? In the absence of hearing any, then I think what we will do is we will take a short break and reconvene at 9:30 to start on the committee discussion again.

Thanks a lot.

[Break.]

Questions from the Committee

and Committee Discussion

DR. WOOD: Let's begin by seeing if there are other issues that the committee want to address from the discussion that we had yesterday and continue that. After that, we will begin looking in detail at the questions so yo might all want to make sure you have them in front of you.

But let's begin with the questions, other issues, other points of discussion, other things that the committee members would like to discuss.

Dr. Benowitz.

DR. BENOWITZ: I just have one question from this morning and that is to get a

clarification from FDA I guess about whether having a pharmacy-only program where the drug can be provided only in pharmacies, is that something which can be done? It sounds like--some people say that that is not provided for in the law. It is proposed be Merck. I just want to know can it be done.

DR. WOOD: Does somebody from the FDA want to take that? Charlie?

DR. GANLEY: I am not a lawyer so I am reluctant to give a definitive, but we have never approved anything in the behind-the-counter.

DR. WOOD: I don't think that is the question. What he is asking is can it be sold in a store that has a pharmacy rather than a convenience store.

DR. GANLEY: That is still an issue of restriction. I misunderstood the question.

DR. WOOD: Maybe, Neal, one way to proceed

would be for the committee to discuss it under that rubric and leave the decision as to how that can be done to the FDA and their negotiators. If we feel strongly, on the other hand, that the drug could be sold in places other than pharmacies, then we ought to give the FDA guidance on that as well.

So it seems to me there are two extremes--three extremes. One is that the drug shouldn't be sold over-the-counter. One is it should be sold in stores that have a pharmacist and one is that it could be sold in any kind of store that can sell over-the-counter drugs.

I guess one of the issues for the committee to debate is which of these options is reasonable and which do they recommend. Is that fair? FDA, is that fair? Bob?

DR. MEYER: I think that is fair. I guess I would just emphasize that one should, in your deliberations, regard the proposal for this pharmacy-care type setting where this is only sold in outlets where there is a pharmacist present as being voluntary.

The reason that I think that is important to realize--you know, we are not saying that we have a definitive answer on that but you should

regard it as voluntary for the purposes of your discussion. Again, the reason that is important is if this drug were to be switched when it were to become a generic drug, that voluntary agreement from the sponsor would no longer necessarily hold for that.

DR. WOOD: Okay; that is a good point. Dr. Fincham?

DR. FINCHAM: I appreciate that clarification. This gets very complex quickly. Even if it is, at first, in a pharmacy that has, quote-unquote, a pharmacist on duty, not all pharmacies that have licenses in any of the states have a restriction on when other types of products may be sold.

For example, you may have outlet that is open 24 hours a day but the pharmacist is present 8 to 10, 12 hours. So what happens when the pharmacist, perhaps, is not on duty. I don't have

the answer to that, but I have not seen anything that would indicate how that would be handled or would be done. I think it is something to at least think about.

DR. WOOD: Dr. Woolf?

DR. WOOLF: Lovastatin is available just generic, is it not? So what would prevent one of the generic companies to say, I want to make this available over-the-counter and what would that do to whatever the paradigm is in terms of educational programs and all those kinds of issues.

DR. WOOD: Somebody from the over-the-counter committee want to answer that?

DR. MEYER: Again, some of this is treading on areas that are difficult for us. The folks here are physicians, not lawyers, so the exclusivity situation, I don't think we would like to speak to. But, to the extent that anything that Merck is proposing is put into their product labeling, that labeling will hold for a generic product as well.

To the extent anything in their program is

not in the labeling, there is a piece of that that you must regard as being voluntary and may not apply to any follow-on products then.

DR. WOOLF: So then the display that was here is not part of their label and that is voluntary.

DR. MEYER: Well, I will let Merck talk to some of that because I see that they are ready to do so. But I think much of that actually would be considered labeling.

DR. WOOD: Dr. Hemwall, do you want to respond?

DR. HEMWALL: Yes. In fact, it is all labeling and it has been submitted as such and would be under total review and approval authority from the FDA. Any changes we would want to make to that would require prior approval before we could make those changes. That includes everything that you have seen in your package and those things that are connected to the package through the proximity in the store may also be considered as labeling.

We obviously commit in that regard. It is

under the NDA. We can't go back on it and neither can a generic. They have to be approved under the same terms. As you heard from the American Pharmacists Association, the pharmacy-care is something that they strongly believe in and, I think, as part of their overall program, they would not authorize a generic to then be outside of the pharmacy-care in the same category which has been deemed pharmacy-care as we have launched it and created it.

DR. WOOD: Do you want to comment on the exclusivity in OTC?

DR. HEMWALL: Pardon me?

DR. WOOD: Do you want to comment on exclusivity in OTC?

DR. HEMWALL: Yes. The exclusivity lasts for three years under Hatch-Waxman.

DR. WOOD: Okay. So a generic could not come--in answer to Dr. Woolf's question, a generic could not appear for three years.

DR. HEMWALL: Correct.

DR. WOOD: Okay. I just wanted to

get--Dr. Bull?

DR. BULL: I just wanted to bring an example to your attention with regard to where you have complex--what are risk management or conditions of approval. Accutane is a drug that has a very, very complex set of documents attached to it for both prescribers and patients. Those are all considered part of the approved label and were part of the conditions of approval. So what Merck alluded to, that their materials are being submitted as part of the labeling, that would then entail those being considered conditions of approval if so approved.

DR. WOOD: Dr. Clapp?

DR. CLAPP: I have some questions that maybe Merck and the FDA can address in terms of labeling of the Mevacor. It is kind of a conundrum and that is if you--you are presuming that you have tried a healthy diet and exercise to reduce your cholesterol, according to the package insert, before you then proceed to take the Mevacor.

Then, once taking the Mevacor, it says,

"If you stop taking it, your cholesterol will go back up." Then am I to presume that if you, then, try harder with a healthy diet and exercise, could that not make Mevacor unnecessary if that change in lifestyle then reduces your cholesterol, and then stopping Mevacor might not make your cholesterol go back up.

But, the other point of concern that I have is then should Mevacor OTC say that if you want to continue to keep your cholesterol within a range of normal you must take every day for the rest of your life. Should it be very clear that there is an expectation that this is a lifelong commitment to medication rather than an intermittent commitment that is based on, I guess, your whim.

I think there was data yesterday that said after two years only 25 percent were continuing statins. I am not sure if that was the over-the-counter--no; it wasn't the over-the-counter. It was prescription statins. So, in the public-health interest, is it

appropriate that we then make it clear to people that, if they take Mevacor, they should consider themselves having a commitment to this medication that is lifelong.

DR. WOOD: I guess a number of people have raised the issue of diet and exercise and the efficacy of it. Somebody maybe ought to comment on that. Tony, do you want to comment on what the actual outcome is with diet and exercise long term.

DR. HEMWALL: Could I have Slide 174 from the core deck, please.

While they are bringing that up, I will answer your other questions with regard to instructions on the label. As you have heard, we have studied consumers very carefully and extensively for a long time before we created the actual final label.

They are very different in the way they approach the information, but one of the things that we have learned is that people sometimes think that, once they get their cholesterol down to goal that they are cured and that they can stop taking

the product. So that is why that message is there, that you will go back up if you stop taking the product.

But, certainly, the program encourages ongoing diet and lifestyle. That is what is found in the materials that come in the accompanying education program and then, of course, in the newsletters that follow, and staying on the product for the duration of the time that you are still getting to goal. That is why the encouragement is to get your cholesterol tested again in a year to make sure you are still at your goal, in which case, you may continue to take it on a yearly basis as you continue to monitor your cholesterol which could extend to a much longer period, as you call it, as a lifetime.

That would be the important thing. Now, I am not answering your question.

DR. CLAPP: The interesting point that you are raising is that your counseling people to change their diet and exercise habits at the same time that you are encouraging them to take the

medication. So if, perhaps, you have a real compliant consumer who is reading your educational materials and decides to change their diet and exercise dramatically--

DR. HEMWALL: Yes; that is a good point. The very first thing on the label--

DR. CLAPP: Excuse me. Let me just finish my question.

DR. HEMWALL: I'm sorry.

DR. CLAPP: Is it accurate to say that their cholesterol will go back up because which factor is it, indeed, that made their cholesterol go down. So who reassesses this and then can we accurately say thatm, if they stop the medication, their cholesterol will go back up if, in fact, they instituted some of the aggressive diet and exercise exercise changes that you are promoting with the medication.

DR. HEMWALL: Those are good points. Here is the way we tried to address that is within the label under the heading, How to Decide if Mevacor is Right for You. Before using, you must have

tried a healthy diet and exercise to reduce your cholesterol. So we are asking people to already take it to that step to make sure that that is already--they have taken it as far as they can. Then, they are to get a fasting cholesterol test within the appropriate period of time and then determine, with that, having tried diet and exercise--and that is exactly what we saw in the type of consumers that are interested in using this product.

I will take the slide now, Slide 174 from the core deck.

[Slide.]

This is a slide you saw yesterday. It is important to point out that these people that came to the site, 80 percent had already previously tried to lower their cholesterol with diet and exercise and, with regard to their change while taking the drug, the change in dietary patterns, 58 percent of them maintained that and another 40 percent, while on the program, did improve. So that could contribute to some of the cholesterol

lowering.

Likewise, in exercise, 70 percent and 0.4 percent improved. So there was no deterioration, as some have speculated, while taking the product.

Could I have core slide 155, please.

[Slide.]

This is the same data. It is shown in another way. You can see that what we did was we administered a MedFix diet test to everybody to really get down to a more technical measure of what their diet was. At baseline, 36 and 47 percent were either on a Step 1 or Step 2 diet, respectively, with 17 percent not on a Step 1 or Step 2 diet. That is the American Heart Association Step 1 or Step 2 diet.

By the end of the study, many had moved up, either from a Step 1 or Step 2 or out of the neither diet so that, by the end of the study, 89 percent were on a Step 1 or Step 2 diet according to the American Heart Association definition. We view this as very, very positive in the sense that we are keeping people to maintain their diet and

exercise and, yes, it may be a component of the lipid-lowering that they get but it is clear that a lot of them have already tried that when they started using the drug.

DR. CLAPP: At that point, did you teas out the difference by continuing the study by stopping those who were taking them Mevacor and seeing whether or not their diet and exercise changes had been a major factor in keeping their cholesterol lower?

DR. HEMWALL: No; we did not. But diet and exercise is usually a few percentage points, 5 to 7 percent. According to some studies, we are talking about a total lowering that was seen here in the order of 20 to 25 percent with lovastatin.

DR. CLAPP: Do you think it is accurate to say, then, that the labeling should--it is appropriate to say that the consumer should understand very clearly that, from your perspective, that, even though they change diet and exercise, that they will need to take Mevacor as a lifelong commitment to keeping their cholesterol

lower? Is that appropriate?

DR. HEMWALL: I think, again, that we could certainly consider that sort of message. But we really want people to continue to check to make sure that other changes in their health status don't require them to see a doctor or that the dose of 20 milligrams of lovastatin is no longer enough for them to achieve their NCEP goal.

So, in other words, we don't want to give the message that all you need to do is take 20 milligrams of lovastatin the rest or your life and you are okay. We want to make sure that there is ongoing reevaluation of their status and what they might need in the future.

DR. WOOD: These are all good points.

Bob, do you want to--

DR. MEYER: I'm sorry. I want to ask a point of clarification on Slide 155 which you just showed. Are those the same patients contributing to the percentages at the beginning as at the end?

DR. HEMWALL: Yes; they are.

DR. MEYER: So these are just people who

completed the study.

DR. HEMWALL: Exactly. So, in other words, for some people, there is just a benefit of diet and exercise even if they didn't continue on with the drug.

DR. WOOD: Dr. Caprio?

DR. CAPRIO: We have been provided with a number of things to read and we have listened to many presentations but, perhaps, I have missed it. I want to know what is the position of the American Heart Association in this matter. If anyone knows it, please share it with us.

DR. WOOD: In their absence, we would have to impute that so I guess we should pass on. That is an interesting question but I am sure they are keen to get cholesterol lowered. Whether they want to weigh in on this is an issue they have obviously debated and decided not to, I think, is the position.

Dr. Benowitz?

DR. BENOWITZ: I just had a very simple follow-up question on the generic OTCs. If there

is an 800 number required for Merck to provide and a generic comes out, and we think that 800 number is important, will that be part of what is required for a generic OTC manufacturer as well?

DR. GANLEY: That is not as easy a question as it seems because we generally don't require 800 numbers. But, as Dr. Bull had said, if that is part of the conditions of approval that we clearly specify is necessary, then it comes down to our lawyers looking at that and agreeing that that is something that would be part of the program.

I know it is not a complete answer. That is the answers we deal with internally, too, when we try to answer these ahead of time.

DR. ORLOFF: Just to follow that up, I think the answer is, however, that it is a possibility. So it is certainly not something that can't happen.

DR. WOOD: I think, again, that comes back to the options we have got and debating which one of these we decide on and then deciding what these are.

Dr. Fincham?

DR. FINCHAM: Thank you. Yesterday afternoon, we heard some presentations regarding

the post-launch surveillance that might occur with lovastatin if it goes OTC in the United States. I am just curious what the company has done in the United Kingdom since last may from a surveillance standpoint.

DR. HEMWALL: We have actually done quite a bit because that was something that is very important and we are planning on learning as much as we can from the U.K. and taking as much of those learnings to the U.S. and implementing a similar system. We have two people from the U.S. on our planning committee there to monitor that, Dr. Randy Juhn and Dr. Valentin Fuster.

I will let Steve Mann give a little more of the details.

DR. MANN: We have undertaken some general-survey work about what has happened so far and I can show you a very small survey if that is of help. But, broadly, we think that the pharmacy

protocol is operating much as we expected. Since that pharmacy protocol was piloted, that is not really a surprise.

What we are more interested in doing going forward is to take a prospective look in a cohort of subjects as to how the actual pharmacy model operates, how the self-medication model operates, in practice. As Ed has said, we have a distinguished body of academics helping us design that study to determine what best to look at.

But, certainly, amongst the items of interest, we will certainly be looking at, firstly, how well the model predicts actual risk by looking at a subset of people and looking at their full risk profile to check that the model is correctly identifying people as we expect it to.

We will, then, also look at how people comply, how they adhere to the treatment and also to their lifestyle measures. We will, in a subgroup of those subjects, also look at LDL-C lowering a surrogate for what we might expect to see in terms of endpoint reduction.

There are various other ideas under discussion but that, certainly, will be the core program of a prospective looking forward.

DR. WOOD: Dr. Davidoff?

DR. DAVIDOFF: I would like to get back to this issue of whether people will maintain their diet and exercise, which is a very interesting question that clearly was on a lot of people's minds. I was quite intrigued by the finding in the CUSTOM study and, in some sense, encouraged or heartened by that because it would be very nice to believe that the decision to take over-the-counter statins might actually encourage people to continue to do things that they ought to be doing anyway that are not pharmacologic.

But I have to also admit that I have substantial concerns about that information in making generalizations from the data that we have seen. In the first place, dietary surveys, even validated ones, they may be reliable but I think, as everyone knows, may not be all that accurate. I mean, in my youth, I ran a diabetes unit and I was

very familiar, spent of lot of time on diet in the nutrition literature. It is quite clear that self-reports of diets are not terribly reliable.

But, even accepting those data, I would also get back to the issue of the sample here because this was a fairly selected sample of people who clearly had, in the first place, responded to an ad to come participate in the study, then self-selected to actually participate, knew they were going to be getting some reimbursement, et cetera, et cetera.

This is not the general U.S. public. If the drug goes over-the-counter, it will be 260 million people who are going to have this available to them. I would argue that the likelihood that this finding in the CUSTOM study applies to that broader sample is not very great and that there may very, very well be people in the general public who began to use over-the-counter statins who, in fact, would feel that this was a magic pill and they wouldn't have to continue to diet and exercise.

DR. WOOD: Dr. Taylor?

DR. TAYLOR: Actually, I would like to take up where Dr. Davidoff left off. I agree with you that the CUSTOM sample is a very narrow sample.

For example, were the advertisements in Spanish? Maybe they were. That is a credit. But I am concerned about the fact that 28 percent of your sample was a non-Caucasian sample. I think--I don't remember; what was a low literacy, how much that was of the sample.

As you know, our U.S. population is in--the non-Caucasian population is growing and, by some date in the future, is projected to be the majority. With that in mind, and given that this CUSTOM study was a self-selected sample, I am wondering if, on all the measures that you had outcomes, like compliance, lower cholesterol, lifestyle changes and that, that that 28 percent perform at the same level.

Do you understand my question?

DR. HEMWALL: Yes; the 28 percent you refer to are the evaluators and then there is a subset of all of those that actually used the

product. I am not sure if we have a breakout by race or gender on diet and exercise. Do we have that?

DR. WOOD: You did show data earlier on minority populations that had a high rate, actually, as I recall.

DR. HEMWALL: This was a very common finding in all of our surveys and those that were done independently by the NLA and the National Consumers League with regard to the type of consumer that is interesting in using a product like this, they are already very health conscious and are doing all the things, like diet and exercise, to manage their health and this is not unusual that this is the type of cross-section that would be interesting in using the product in the CUSTOM study.

So we don't necessarily agree that it is a narrow band of people that doesn't represent the group that would use it in the real-world marketplace.

DR. TAYLOR: One other question. In your

pharmacy promotional information, your pharmacy intervention, how would you ensure that there would be language compatibilities at the point of sale of the product?

DR. HEMWALL: Language compatibilities? Are you speaking Hispanic?

DR. TAYLOR: Hispanic.

DR. HEMWALL: Yes. Actually, Johnson & Johnson and J&J Merck are very committed to reaching out and marketing to the Spanish community and have a number of programs already in place for the programs, or the projects, that are already available OTC. In fact, we are launching a Spanish label for Pepsid AC this month and we have already had Spanish-language advertising. We intend to have that same level of Hispanic community reach-out and other minority communities as well for a product like this.

DR. TAYLOR: But what about at the point of sale?

DR. HEMWALL: In neighborhoods where the language is predominantly Spanish, we would have

Spanish materials.

DR. TAYLOR: But pharmacy intervention is a critical part of what you are proposing.

DR. HEMWALL: Yes; and it would be only in pharmacies so it would be in the pharmacists and in Hispanic--

DR. TAYLOR: But would there be staff who would be bilingual or be able to communicate? Many of the patients that I see that are Hispanic don't speak any English.

DR. HEMWALL: I don't have an answer for whether or not individual pharmacies, in those communities, would have bilingual pharmacists.

DR. TAYLOR: But, as a part of what you proposing, I think that is a consideration.

DR. HEMWALL: I think it is a good idea and that would be something we would want to make sure that we have the proper training and the materials in both languages.

DR. WOOD: Dr. Patten, do you want to comment on this?

DR. PATTEN: We have heard survey results

indicating that the general public considers OTC medications to be less risky than prescription medications. That being the case, I am wondering if there is any information available, or if it has already been presented, I missed it and I would like to revisit it, what are the consequences of starting and stopping and starting and stopping a statin.

I am guessing that, if it goes OTC, that will happen fairly frequently as people run out, it is a week or two before they get back to the drugstore or the pharmacy, or they are pinched for money this month so this is something that goes by the board.

So I am wondering what the health consequences are for starting and stopping, starting and stopping, this medication at this strength.

DR. WOOD: So the question is are there adverse effects of starting and stopping or are there beneficial effects in inadequate--

DR. PATTEN: Right. What happens to lipid

levels? Do they go up and down and up down and what are the health consequences.

DR. WOOD: Dr. Gotto?

DR. GOTTO: Tony Gotto. There is no credible evidence that stopping a statin causes a rebound or any increase in risk if the risk is related to the LDL cholesterol level. As the cholesterol and LDL go back to baseline, you would lose the benefit of having the LDL reduced.

But you can be sure that when you stop it, it will go back up into--related to the previous concern, I would have a concern if you had a statement that led somebody to think if they took it and, for some reason, had to stop it, it would cause some immediate reaction, have some health consequence such as stopping, abruptly stopping a drug like clonodine.

So that is not the case with the statin. It is a lifetime recommendation in a sense that it only is effective as long as you take it in lowering cholesterol. Now, if the AFCAPS/TexCAPS study, we did see a benefit for two years after the

study was over, an increased reduction in cardiovascular events and also there was a benefit within the first year.

But the lipid levels are going to go back up either if you go off your diet or exercise program or if you stop taking the medication.

There have been two studies comparing statins with diet. One, Hunninghake and colleagues published in the New England Journal of Medicine in which they had a patient on lovastatin in one group and on an American Heart Association diet, and there was about a 25 percent or so change with the lovastatin group and about a 5 to 6 percent change in the American Heart Association.

There was a subsequent publication about two years ago with a much more extreme diet, very large amounts of fiber, nuts. It was an atypical diet. But at least you can concoct and put together a diet which, in that case, gave the same, approximately the same, amount of reduction of LDL as lovastatin.

The diet, the exercise and the medication

all work together. I think the over-the-counter Mevacor is aimed for healthy people who have an interest and want to diet and exercise but need something more than that to get down to their target LDL levels, at least that is the intended population. Those are the recommendations. So this makes something available for an individual who is not able to get there but with a combination of diet, exercise and medication may be able to achieve their target and reduce their cardiovascular risk.

DR. WOOD: But, while you are up, isn't it also true that only a very small proportion of patients who have a validated risk are able to adequately reduce their risk with diet and exercise alone?

DR. GOTTO: It depends on how much the LDL is elevated.

DR. WOOD: Right. But I meant, with elevated risk due to LDL.

DR. GOTTO: Yes. Yes; if they have got a markedly abnormal LDL, that is correct. It is

difficult, also, to get patients to follow a diet, exercise or take a medication over a period of time and you are right. Most patients are not able to maintain diet sufficiently adequate to keep their LDLs in range.

There are some publications, Frank, that there is a correlation, positive correlation, between both diet-and-exercise adherence as well as medication with the other two so that an individual--people who were followed over a period of time on a diet are more likely to maintain the diet if they are also exercising.

They are also more likely to maintain adherence to their medication if they diet and exercise. So I think there is a correlation probably related to the type of individuals who go into a program of prevention to begin with.

DR. WOOD: They are people who know all about everything; right?

Dr. Follman, did you want to comment directly on that?

DR. FOLLMAN: I wanted to talk a little

bit about the on-and-off aspect. There is concern maybe that use of Mevacor might be intermittent. The discussion around this is focused on what would the risk benefit be for an individual due to statin interruption and then reintroduction.

I am thinking of a different kind of potential risk would be, say, call it desensitization where an individual, because they have tried a statin and given up on it, will, in future, be less inclined to seek a doctor the period of time when their LDL is really quite high and they really need it.

So the fact that they used a statin and had forgotten about and thought, oh, I have tried that statin thing. I don't need it anymore. When they really need it, it is no longer available. It changes their future health-seeking behavior, if you will. So I am wondering if that has been thought about, if it is a concern or not.

DR. WOOD: Dr. Snodgrass?

DR. SNODGRASS: My question is regarding the CUSTOM study and maybe both FDA and Merck could

address this. In the low-literacy group, I thought it was about 11 percent, was there a subanalysis of the low-literacy group with regard to correct choice?

MR. TIPPING: This is Bob Tipping, again. We did look at the behavioral results from CUSTOM in a number of subgroups, the low-lits, difference in race, differences in age. But, specifically, to your question about low literacy, there are 12 percent of the users who were classified as low-literacy based on the REALM test and the behavior was consistent that the behavior against the self-selection messages and the behavior around the decisions to stop use were consistent in that 12 percent subgroup.

DR. WOOD: Dr. Carpenter?

DR. CARPENTER: Another concern much like Dr. Follman's regarding the episodic use of statins, is there any evidence about refractoriness to either subsequent courses of statins or alternative behavioral methods of lipid control following multiple on-and-off courses.

DR. WOOD: So the pharmacological desensitization.

DR. CARPENTER: Correct.

DR. WOOD: I guess the answer is no, but someone else may want to answer that.

DR. PASTERNAK: There is considerable evidence that there is no resistance that is developed by going on and off because, in the course of studying all of these drugs, not just Merck but all of the pharmaceutical companies studying statins, many of the trials are, in fact, done exactly that way with on-and-off periods.

DR. CARPENTER: Thanks. A second question has to do with anecdotal comments I have heard about abuse of statins in eating disorders. I wondered if there is any other potential for abuse of these medications.

DR. WOOD: Let's just make sure people understand the question. There is a suggestion that particularly young women abuse statins sometimes because they believe that fat is bad and something that reduces fat will make them slimmer.

Is that a fair summary of what you are trying to ask?

DR. CARPENTER: Correct.

DR. WOOD: Okay. Does anyone have data on that one way or the other?

DR. CARPENTER: Or other potential areas of abuse of these medications.

DR. WOOD: But maybe a statement that it doesn't do that would be helpful.

DR. HEMWALL: I don't even know the reports that you are talking about so I--do any of our experts? Have they heard of this before? No.

DR. CARPENTER: This is not published.

DR. HEMWALL: It may be something one would try but it probably doesn't work, so the positive reinforcement wouldn't be there.

DR. WOOD: Dr. Clapp?

DR. CLAPP: I wondered if Merck has done any postmarketing research from when you direct-market to consumers a medication like you said Prevacid, have you studied to see whether or not consumer behavior is appropriate in terms of

the usage in determination that their purchase is appropriate for the complaint that they have and, if so, could you extrapolate that to consumer behavior that you predict, not just from the CUSTOM study but--how does direct marketing to the consumer affect purchase behavior that differs from solicitation for a study like the CUSTOM study?

MR. HANSON: I don't have the exact data but I can tell you Johnson & Johnson had to switch a monostat. We have been doing postmarketing studies on monostat since its approval around 1990. So, as it went from 7-day to 5-day to 1-day to cream to pill, each one of those has been done, looked at, from a postmarketing standpoint in conjunction with the FDA.

So, if there are any issues, we certainly go back and address those. I just don't have the data. But there is precedent for postmarketing with an OTC.

DR. WOOD: Dr. Tinetti?

DR. TINETTI: My question relates to yesterday when we heard about the treatment gap. I

interpreted the data that the benefit to the population, because the benefit to the individual is pretty small, given their absolute risk of having an adverse event, was predicated on the total population who are eligible for this medication having access to it.

This morning, when we were concerned about some safety issues, I heard a much narrower definition that it would only be the people who are "interested in their health" and have high health literacy that would be most likely the people that would access this medication.

So I guess I would appreciate some comment from the people, who they really think the target group is for this medication and how that actually affects the public-health benefit. It would certainly mean we need to know what percent of the population meet the criteria that you just mentioned would probably be the takers of this medication.

DR. WOOD: So your question is, is it aimed at people with the anal group or the people

without health insurance?

DR. TINETTI: No. Yesterday, we heard that it was aimed at the entire population of people who meet criteria. In response to Dr. Davidoff's comment, it was concern about people taking this medication and whether or not they would stop exercising and diet, et cetera.

We heard that probably the people that would take this medication are those who are overall adherers. That is my question, which--we are hearing two sets of target population and what effect, which one do they really think and what do they really think is going to be total public-health benefit.

DR. PASTERNAK: It is, I think, a semantic point and I think we will have a two-part answer today. The target remains the target. The target is the target as defined by NCEP, ATP 3 is moderately high in moderate-risk people. So that is the target.

The question, though, and I think it is important one, goes to who, among that target, are

likely to use it. That is not target. That is use. And that is where we have information to share with you.

MR. HANSON: I would like to look at slide 1978.

[Slide.]

As Dr. Pasternak said, we are targeting everybody who is at moderate risk treatment-gap section. However, we have found, and I mentioned the 34,000 people we have talked to in the past seven years, very strong consistency in the market research we have done, quantitatively as well as the CUSTOM study.

I think this is very relevant for a lot of the discussions that have taken place today because it shows along each of the columns some of the issues discussed. So what this looks at are these are the likely people who are likely to take action and try and OTC. You will see whether it was done with market research, done by Merck or done by outside organizations with regards to diet and exercise, their doctor visits, whether they are

likely to see a doctor in using this, whether they use vitamins and supplements. Everything is very consistent.

So, although we are targeting a population that is 15 to 20 million, what our research says is it is going to be much more selective than that. It is going to be these people who are interested--

DR. TINETTI: What number is that?

MR. HANSON: That will in the range of 3 million to 5 million people. Again, that is very rough.

DR. TINETTI: So, if it is 3 million to 5 million, then how does that translate into the population benefit of this medication?

MR. HANSON: I will ask Dr. Cohen to address this, show this, from his core slide.

DR. WOOD: Just before you leave, presumably, of course, that is all predicated before an advertising blitz starts.

MR. HANSON: Actually, these studies simulate what will happen with advertising because we actually do these to forecast sales from a

business standpoint. So what we do is we show consumers an advertisement, simulated advertisement, in a general population.

DR. WOOD: No, no,no. I understand that. But if you start advertising OTC medicines, then groups that have not thought about lowering their cholesterol will be exposed to that in a way that they have not been up to now.

MR. HANSON: That's true. But the way we simulate this is we do go to a general population, whether they are interested in cholesterol or not. We show them an advertisement for OTC cholesterol. We tell them the price and the numbers that I am quoting are the ones that say, after I have seen that, whether I am interested or not, these are the ones that say they are going to buy.

It is not real-life but we try to simulate--

DR. WOOD: If you went out and asked people about TEVOs and, if they have never heard of TEVO, they won't know about it. If you have an advertising blitz for it, you will know about it.

So you extend your proportion of people enormously at that point.

DR. COHEN: Jerry Cohen. Thank you. That is a good question. Just to reiterate, yesterday, I identified the treatment gap and the size of that gap was between 6 million and 15 million people in the moderate-risk group. What we estimated was, in that gap that we have identified by the label, approximately 3 million to 5 million additional people will come on to therapy.

When we look at the public-health benefits, it applies to that group. As I mentioned yesterday, this is not a panacea. It is not going to fix the entire treatment gap. But if we have a million patient years, a million people using the drug over the ten years estimated, we would see a reduction between 20,000 and 35,000 coronary events. That is the huge public-health impact.

DR. TINETTI: What adherence rate did you use to calculate that?

DR. COHEN: We used an adherence rate of people persistently taking the drug.

DR. TINETTI: For ten years.

DR. COHEN: Yes.

DR. TINETTI: 100 percent.

DR. COHEN: Per 1 million. That is for just a million. If it is 3 million who continue to persistence over the ten years, you can multiply the 25 times 3, et cetera. Or you can reduce it proportionately as you wish.

DR. TINETTI: So, in the perfect--

DR. COHEN: But that means persistent taking ten years, a million patients, this is what we would see. And we saw earlier the persistence data is very, very good. It is just as good as was pointed out earlier in the Rx treatment.

DR. TINETTI: The only persistence data we have are randomized controlled trials over five years, not actual use.

DR. COHEN: The CUSTOM data that was shown--

DR. TINETTI: That was only for six months.

DR. COHEN: Six months; correct.

DR. TINETTI: That is only six months which doesn't tell us very much about ten years.

DR. WOOD: Are you finished with your response?

DR. COHEN: Yes.

DR. WOOD: Dr. Clyburn: That was actually

my question but I want to follow up a little bit. When we talk about target populations, the vast majority of the patients in the CUSTOM study didn't meet your eligibility requirements. So does that modeling hold true given that the vast majority may not be in that moderate-risk population?

DR. HEMWALL: The model that Dr. Cohen described applied the exact parameters of the CUSTOM population, the CUSTOM population, itself, not the target population.

DR. WOOD: Dr. Schambelan.

DR. SCHAMBELAN: This is probably an early question, but, since you have had six months experience in the U.K. and I realize that you are planning to do an assessment of outcomes, do you have any idea what the sales have been and, in

particular, what is the target population in the U.K. compared to the 3 million to 5 million that we have heard about here in the U.S.? Six months.

DR. MANN: I have to say, what we have tried to do in the U.K. is a staged approach to this. Our first concern has been to make sure that the model in the pharmacies is working so that when people are stimulated to go in and talk about this that they get a good response.

So we have really concentrated on that for the moment. Television advertising has only begun on Boxing Day, the 26th of December of last year. So I think it is early to say what the consumer response will be.

I think it is fair to say, though, that in the U.K., because we are starting from a level of population knowledge about coronary heart disease that is probably considerably less than it is in the United States, we do expect it to be a fairly slow build and we anticipate a lot of education being needed on a population level to get people to understand that this is a concept that may apply to

them.

But, in terms of the total population, the total population gap, proportionately, in terms of the population, it is very similar to the United States.

DR. WOOD: Dr. Parker and then Dr. Follman.

DR. PARKER: I wanted to talk for a couple minutes and hear where the FDA might be as well as where the sponsor might be on the issue relating to advertising. Obviously, we have the results of the actual-use study which show us that there were many people who self-selected incorrectly for whatever reason. My guess would be they didn't understand what they needed to do and it seemed like maybe it would be a good idea.

So, perhaps, there was some sort of persuasion that led them to decide to do this. I am not really sure because we don't know a lot about those people. I would like to know a whole lot about those people because that really concerns me. But we don't have a lot of information on

that.

But I know that, were this product to go over-the-counter, it would be heavily advertised. There is a slippery slope, however you define it, between advertising and educating the public.

The requirements for the label are that the ordinary person can understand what they need to know based on what they read on the label. I think the actual use calls to question the ability of many people to be able to do that.

Advertising takes it to a new level. There was some mention yesterday of perhaps--and advertising is not under the control of the FDA. It is under the control of the FTC. So I am wondering--there was a slight mention yesterday that perhaps looking at the FDA having a stronger role in regulations regarding the advertising, and I am wondering, perhaps, how the FDA feels about that. But I would also wonder whether or not the sponsor might be willing to partner with FDA in trying to see that happen.

DR. WOOD: I doubt the FDA is going to

answer that.

DR. GANLEY: Please write to your Congressman.

DR. WOOD: Right. I thought that. So the message is advertising should be under FDA control but there is not a public statement to that effect from anyone.

Dr. Follman. If there is anyone else wants to talk before we start on the questions, you had better indicate it now. Go ahead.

DR. FOLLMAN: I wanted to talk a little more about the treatment gap and the potential for underdosing. Dr. Cohen just mentioned--we had a brief discussion about the 1 or 2 or 3 million people that they expect would be brought in who are moderate risk under an over-the-counter program. The presumption is, and I think it is a fair presumption, is that they would get benefit from receiving a statin. I think that is unquestioned.

So we can do some calculations. Actually, the calculations I will be describing briefly are, given an article by Dr. Brass and so I am changing

them slightly, but I think they will help inform the discussion now.

If we have an individual who is in the center of the target for Mevacor OTC, say, with an LDL of 150, and they have a Framingham risk score of 0.15, and they are brought in to use over-the-counter Mevacor, their risk will go down by about 20 percent, say. So the risk of death will go from 0.15 to about 0.12.

If we translate that to 100 people that are brought in, we would expect three fewer CHD events for these people that are brought in. So that is on the plus side. There is no question in my mind about that.

On the downside, though, there is a concern which is mentioned in Dr. Brass' article about underdosing. So, in the CUSTOM study, we did see that about a third of the patients had LDLs larger than 170. So, if they had optimal therapy, they would reduce their risk even more than they would reduce it with Mevacor at 20 milligrams. So the calculation you can do is you assume that a

person with a Framingham risk score who is inappropriately taking over-the-counter medication reduces his risk by a little bit so it will go down to about 24 percent.

If that person is optimally treated, his risk will be cut in about half and his risk of death will be about 15 percent. So if we bring in 100 people into OTC over-the-counter therapy when, in fact, they would have been getting optimal prescription therapy, we have caused nine more deaths.

So, to balance this in a simple way, you could say, if we bring in three new people, moderate risk, for which it is intended, but we also bring in one person who should be on optimal therapy but is now getting Mevacor over-the-counter, we are indifferent in terms of the population-based risk:benefit here.

So it is not just bringing in these people. There is this concern about underdosing.

Now, I should say that these calculations I have described here which were also given in Dr.

Brass's article, are, under certain assumptions, a person with an LDL of 150 versus 200 and so on. But the important point, I think, not to get too specific, is that there will be some underdosing and it is much worse to have a person go from optimal therapy, or what would have been optimal therapy, to under-therapy. That is worse than bringing in someone who is at low to moderate risk into something that gives him a moderate benefit.

DR. WOOD: That is true, of course, but just to make the other side of that case, every one of these people had the opportunity to get prescription therapy right now and, for whatever reason, didn't avail themselves of that opportunity. I guess, secondly, perfection is the enemy of the good. People are not being denied therapy because of that. It is that they are not currently, for reasons we don't fully understand, I guess, are not availing them of that right now.

DR. FOLLMAN: It is a fair point. So, like the person in Arizona Dr. Schade alluded to yesterday who is at high risk and not going to do

anything, if he is not going to go get prescription statin and he does get a statin maybe underdosed with OTC, that is in that plus, too. So we don't really know the full dimensions of this.

There is some concern about under-dosing. It is complicated and I just want to frame the argument here and point out that under-dosing is more of a concern, I think, than bringing in people who would not be getting statins otherwise in the moderate-risk group.

DR. WOOD: I am not sure I understand that. I am going to keep that line of conversation going. I mean, by offering therapy to people, you don't preclude others who should avail themselves of a different therapy from getting it from their doctor.

DR. FOLLMAN: No, you don't. But--

DR. WOOD: Hang on. There is a sort of philosophical issue here, sort of almost libertarian issue, that should you deny the right to people who want to take something because other people are behaving inappropriately. That is an

issue the committee is actually going to have to grapple with, I think.

The people who have LDL's over 170, which I thought was interesting in the sponsor's document. There were people in there with LDLs that were extraordinarily high and, interestingly, these people seemed to consult their doctor and get advice about which 3A4 inhibitors they shouldn't be taking which seemed improbable to me, that if the doctor hadn't treated their LDL. That these same doctors were sort of experts on drug interactions just seemed to me a little hard for me to swallow.

But I was surprised that they didn't sort of raise that. I am grappling with that but I am not sure that we have exhausted that topic. So go ahead.

DR. FOLLMAN: I think that is an extremely common concern initially. In fact, when I first heard about this option and when colleagues, clinical colleagues, of mine react to it, the concern is exactly what was just stated. I think the data, both the data from studies that were

submitted to this panel in 2000 and in CUSTOM suggest, however, that that concern is invalid, that, as Dr. Wood just said, this is not taking people away from the medical system.

You can debate how much it is driving them into it but there is no evidence that it is taking people out of that. In terms of the medical system, even former Presidents being cared for by physicians stop taking their statins.

DR. WOOD: Apparently on their physicians' advice, we were told in the paper. Sorry; I will let you finish. Go ahead.

DR. FOLLMAN: Just to finish up. These studies are all done in the prescriptions world and so people who do come into the CUSTOM study, et cetera, weren't getting statins. I am thinking about the individual in this over-the-counter world who would have seen a doctor and gotten optimally dosed but, in this hypothetical over-the-counter world, he doesn't bother to see a doctor. He thinks, well, I will take care of it myself with Mevacor over-the-counter, and, hence, he is

underdosed.

So there is this concern. The studies that were done have been done in this prescription world. I don't think we really know to what extent this will be a problem, in which way the balance will tilt at the end of the day.

DR. WOOD: Okay. Good point.

Two more questions and then we are going to turn to the FDA's questions unless there are people with compelling points. Now is your moment.

Dr. Woolf.

DR. WOOLF: I would like to come back to the issue of teratogenicity that was raised yesterday and we were provided with a lot more data this morning. Back of the envelope, we are told that roughly there are 5 million Americans who are likely to use the product the way the company hopes it will.

There are roughly 5 percent of the CUSTOM women were 40 to 45 years of age. I have no idea what their fertility rate is but that is roughly a quarter of a million women. Some of them will get

pregnant on this drug and there are some concerns that were raised this morning that, I don't think, certainly, can be ignored. We don't know what the magnitude is but I don't think it is trivial.

So I wonder, given this information, what the company will do when this goes out into the real world and people can walk past the display and say, oh; I think I am going to improve my heart for the future and take the drug without really looking at it quite as closely as they need to.

DR. WOOD: So you are talking about the pregnancy risk.

DR. WOOLF: Yes.

DR. WOOD: We are going to come to that under Question 4. Just to keep us moving, I think we are going to have plenty of discussion, I suspect, at that time. So would you be agreeable to deferring that until we get to that actually on the questions.

DR. WOOLF: Absolutely.

DR. WOOD: Dr. Benowitz.

DR. BENOWITZ: I wanted to ask and follow

up on a comment I think Dr. Wolfe made about a potential adverse effect of peripheral neuropathy quoting three case-control studies. This was something that we hadn't heard about before and I was not aware of it. I am just curious to know more about that, what the data look like.

DR. WOOD: Who was it that quoted it? Oh; Sidney Wolfe. Okay.

DR. LEVINE: A lot of these studies are hard to interpret because a lot of these patients who are taking statins are also diabetic or have other things, and they have peripheral neuropathy from that.

We actually have looked at EXCEL and AFCAPS for peripheral-neuropathy adverse events and there is no difference between actives and placebo. In our WAYS database, actually, the reporting rate--we have about 363 reports on peripheral neuropathy and, with the 27 million patient treatment years, the reporting rate comes out to 1.34 reports per 100,000 patient treatment years and the background rate is 7 to 15 cases per

100,000 years.

So our reporting rate is less than what the background treatment rate--if there is an association, it seems to be very rare. I think the benefit would outweigh the risk.

DR. BENOWITZ: I am just curious. What were the odds ratios in those three case-control studies? Were these large odds ratios or small of what? I have no idea what any of the studies showed.

DR. LEVINE: I don't know. I just have our data.

DR. WOOD: Does the FDA know that? Is it currently in the warnings or precautions?

DR. ORLOFF: No; but I think we would agree with the sponsor's assessment.

DR. WOOD: All right.

Dr. Neill?

DR. NEILL: Because I think we are going to be discussing these eight questions real quickly and because I find myself rethinking same thoughts at each question and because I believe each of us,

as a committee and probably audience members, are interested in having this be as focused a discussion as possible, I feel compelled to just share briefly some of the concerns that I have.

First, I want to summarize what I have heard over the last day and a half. First, this is a large public-health problem and that it can be fixed by taking Mevacor OTC it is going to fill a treatment gap and we are going to increase, even, people who are high risk taking statins and that is an added benefit and, because we have failed to meet that public-health goal of increasing the numbers of people on statin, we are being asked to consider implicitly, if not explicitly, changing what constitutes the OTC-ness of a condition, and, instead of focusing on relief of symptoms, self-diagnosis and monitoring and the ability to carry this out in the absence of a learned intermediary, we are going to be focusing, instead, on a patient's ability to self-select, the ability to adhere to recommendations from a box and the ability to access a learned intermediary when

needed.

Implicit in each of these is a risk:benefit ratio for an individual patient that is favorable across the board.

I have also heard that this switch would be safe, although there are questions about interactions with the number of medications and other herbal preparations and questions about its use in pregnancy. I have heard that, even if it is not safe, that the people who don't self-select or who might not appropriately self-select using those other meds or being pregnant are probably going to benefit anyway. I will be honest. I think that may be true.

I have heard that it is effective based on AFCAPS/TexCAPS data that, I fear, is not generalizable to the OTC setting and is based on a proxy LDL measure of use over six months rather than a real outcome of interest to me which is whether my patients live longer or suffer fewer heart attacks or strokes.

I also have heard that patients can

self-select appropriately and that, if they do make a mistake, as I said, that they will still get from benefit.

Lastly, I have heard that patients adhere, if only for six months. One thing I have learned as a family physician is that I no longer ever say to a patient, you must be on this medicine for the rest of your life. There are two reasons for that. The first is something better always comes along. The second is sometimes we know better and you have got to change for that reason.

Unfortunately, both for the FDA and for Merck, sometimes we know better and medicines leave the market. Unfortunately, when something new comes along, it typically is always more costly and less available to the patients.

Now, we are about to talk about eight questions and we have been given some very careful guidance from the FDA almost like jury instructions. I was talking with one of staff earlier in terms of how we will think about these things. The good thing about being a jury is, once

we get the instructions, unlike the FDA that cannot and does not consider cost or public-health benefit, we can pretty much consider what we wish to.

The kinds of things that I consider are that having more people on Mevacor would improve the public health and I honestly believe that that is the case. And I believe that Merck, as a company, deserves a lot of praise, both for bringing this class of medicines to the market, for innovating, for taking the risks to even ask this important question, should we consider a new class of OTC.

If we have failed so miserably in the public-health arena as to have this many people not being adequately treated, then is this something that we could try instead. And that is, I think, a real and valid question. It is not going to be answered by this group but it is a good question to bring up and I am sorry if, in some respects, Merck ends up as a whipping boy because your history, as a company, does not deserve that. You are some

good folk.

Okay. Having said that, I do have one last--sorry--I recognize that there are some other motivations that are at work here. I recognize that there is an interest in expanding a market share. This is a good thing if it gets more people on medicine.

I realize that there is an interest in increasing marketshare, however big it may be, and that somebody is going to get three years of exclusive rights to OTC marketing, and I do believe marketing will happen.

Lastly, I recognize that the changing OTC Mevacor is only one way that we can meet this important public-health goal. We have heard about a lot of others including health and diet and I trust that most of you listening, like my patients and like myself, understand that it is hard to do the right thing when you are reaching for ice cream in the refrigerator, when you sit in a meeting for two straight days and don't really have the time to do the physical activity that we are told by the

federal government we would be doing every day.

As a result, I don't think that this is an appropriate way to address this important public-health issue. It is not an appropriate model for other chronic-illness management. I would not be interested in sitting through meetings about anti-hypertensives and oral anti-diabetic medications. We do not know enough about the ability of mass-market campaigns to effect change at the public-health level.

What we do know is that, despite JNC7 and NCEP and all of the other federal and public-health programs that have been around to bring these kinds of issues to the awareness of the American public and that have cost a lot of taxpayer dollars, there are other efforts--Atkins comes to mind--that have not only made money but have been more effective at bringing these messages in front of the people.

Perhaps competition is a good thing in this regard. That is another reason why I applaud Merck for asking this really tough question. I think having competition across the market is a

good thing but the best way to handle this is through some kind of coordinated public-health marketing effort.

I am a little saddened that FTC and FDA can't speak, that HHS or we, as the public, can't get to the point where we can discuss, in some controlled and considered way, things that, in the U.K., have been able to be discussed. I appreciate that, in the U.K., Zocor is OTC. I think it is wonderful. Many things about what happens in the U.K. I would love to have here. They spend a fraction of their GNP on what we spend.

Without talking about the value that they get for that dollar, if nothing else, if, by switching to OTC, I could get some agreement that we are going to reduce our overall health spending to that sort of level, I would say, great. Let's go for it.

Now that I have got that off my chest, I am going to be as quiet as I can for the rest of the day. Thank you.

DR. WOOD: Okay. Looking at the weather

outside, you could feel right at home in the U.K.

The final word before we take the questions is from Dr. Patten.

DR. PATTEN: Thank you and I am sure my question will not be nearly as eloquent as my predecessor here. I have a couple of questions about the possibility of inappropriate dosing and I would like to refer back to the hypothetical patient that comes in with an LDL above 170 but makes the decision to use Mevacor OTC.

What are the possibilities that a pharmaceutical aid, let's say, would say to the person, well, just take two a day, or that the person, himself or herself, would conclude, well, I will just take two a day.

So, if you have a person on what amounts to OTC 40 milligrams a day, what are the possible consequences to be taking that dose relatively unsupervised.

My other question about inappropriate dosing has to do with the person who is within the desired range but we are talking about people very

concerned about their health. I am asking about a person who might fall into the category of the worried well.

There is a great deal of information available to the public about, "lower it; lower it; lower it; the lower the better." So someone decides, well, I will just buy myself this little added increment here of health or safety or risk aversion. Has there been an arm of a clinical trial looking at impact of 20 milligrams over a sustained period of time on a person whose LDL is already in the optimal range?

DR. HEMWALL: There are a lot of questions contained in there. I will try and address them.

DR. WOOD: Let me try and summarize what I think I heard the questions.

DR. HEMWALL: Okay.

DR. WOOD: Is there a risk from taking more than one tablet a day, namely two, and you might want to put in context the prescription dose is up to 80 milligrams.

DR. HEMWALL: That's correct. The

prescription dose is up to 80 milligrams and I think that if someone were to take--on the question of whether or not they should be doubling up on dose which, by the way, we found very, very little evidence of in the CUSTOM study, the question might be raised, No. 1, the doubling of dose only gets you another 6 percent of lowering so it is not like a doubling of effect. That is just in terms of the pharmacology.

Second, if someone is being advised along those lines, they would probably also consider the economic impact in that buying two boxes a month of an OTC 20-milligram dose is probably going to be more expensive than getting generic paid out-of-pocket for even a 40 or 80-milligram dose in prescription. So there would be an economic disincentive to actually behave in that way.

The second part of the question was related to if someone was lower in the range, say, even below 130, and they took 20 milligrams for an extended period of time, I believe there is a large body of evidence that says even those folks would

benefit although their absolute reduction may be relatively less because they are starting at a lower level of risk.

Certainly, Dr. Pasternak could address that further, but there would still be benefit.

DR. PATTEN: What was the nature of the question in the CUSTOM study that got at this issue, whether or not a person would ever consider taking more than one of these a day. Was that specifically asked?

DR. HEMWALL: We monitored how many boxes they purchased and how many pills they returned at the end of the study and then tried to do the calculation of how many days they were actually on drug.

Now, one of the things that we had to keep hands off on with the consumers was actually keeping a diary card because, once you ask them to keep a diary card, then you are taking away the hands-off approach and you are trading an artificialness which has them actually marking every day that they took the pill which would,

then, possibly be criticized for not being realistic and naturalistic.

DR. GANLEY: Can I just follow up on that because I think she asked a very important question and I am not sure it was directly answered. It is a population of people who have what would be considered a normal LDL or a low LDL and take the medicine for a prolonged period of time. Are there adverse events associated with that that we are not aware of because that is generally not the population who sees it on the prescription side.

So it is a very important question because there are a lot of people out there that take dietary supplements for their cholesterol health. These people may get pulled into this. So I think it is important to understand are there any data that has looked at that.

That is, I think, what your question was trying to get at.

DR. WOOD: I guess there are data that have looked at driving the LDL down to 70 and 80. So maybe we should hear that.

DR. GOTTO: There are patients, people, who have familial hypobiliuric proteinemia who go through life with levels, very low levels, of

cholesterol and LDL and, except for some minor transport abnormalities across the red blood-cell membrane, there are no abnormalities that you can detect with having very low levels of cholesterol or LDL.

In a number of the trials that are either ongoing or some I have been involved with such as the MIRACLE trial and the PROVEIT trial where there were very low levels of LDL, there was no toxicity associated with it.

So I think, at 20 milligrams of Mevacor, there is no clinical evidence that taking 20 milligrams of Mevacor in someone who is below the range will do any harm.

DR. WOOD: Aren't there data that you addressed that getting your LDL down 70 may have some benefit.

DR. GOTTO: Yes. That certainly is the case and some of the patients in the Heart

Protection study had lowere levels. Then the PROVEIT study, with acute coronary syndrome patients having a LDL of 70 was better than--or 64, actually, was better than having one at 94.

DR. WOOD: Just to reassure people, and this is a question, there does not appear to be any generic--unfortunately choice of word--but any generic adverse effect of driving your LDL down to, say, 70.

DR. GOTTO: That's correct.

DR. WOOD: Then let's move on to the questions.

Questions to the Committee

In order to try and get us to go through these as efficiently as possible, what I would like to suggest we do is we try to confine our discussion to each question as we address it directly. You will see other issues come down below, but let's try and avoid bringing these up until we get to that question, just to try and focus what we are talking about.

The first question, which you should all

have in front of you, and I will read it to you; taking into consideration the efficacy data from the various trials plus any additional information, and I would remove "provided by the sponsor" because there is plenty of other information as well, please respond to the following questions. Firstly, does the proposed target population merit treatment with a statin to lower cholesterol and thereby reduce heart-disease risk? Secondly, has the sponsor provided adequate rationale for the use of the fixed dose of lovastatin 20 milligrams to lower cholesterol and heart-disease risk in this population? I would ignore the example right now because I think there are other issues there, too.

So, let's start with Question a.; does the proposed target population merit treatment with a statin to lower cholesterol and thereby reduce heart-disease risk. Discussion? Sorry, David; do you want--

DR. ORLOFF: I just want to give two minutes on the way these questions were structured, just to be sure.

DR. WOOD: Start the clock. Just kidding.

DR. ORLOFF: So that I hope there can be less confusion. The first four questions really

relate to the intrinsic safety and efficacy qualities of the drug at the dose proposed and ask for judgment based upon the review of the data presented, recognizing, of course, that there are data lacking, specifically, to answer these questions where true judgment is necessary, but for your best answer on these. So these are intrinsic qualities of safety and efficacy of the drug.

Questions 5, 6 and 7 go to the CUSTOM actual-use study results. We ask for your judgment as to what those results imply with regard to the safety and efficacy of Mevacor OTC according to the proposed program.

Then, of course, the last question is the ultimate one.

DR. WOOD: As they say. All right. Is that helpful to people? Are there any other questions you want to ask the FDA directly before we begin the discussion that would clarify your

understanding of what we are supposed to be doing? In the absence of that, let's move ahead. Any discussion? Okay. Nobody wants to discuss this before we answer the question?

Let's move through the question then; does the proposed target population merit treatment with a statin to lower cholesterol and thereby lower risk. Am I right that Dr. Ryder can't vote? So we will start with Dr. Woolf.

DR. WOOLF: My answer is yes.

DR. BENOWITZ: I would say yes but only in the context of the sort of compliance that was seen in clinical trials taking the drug for five years.

DR. ORLOFF: Again, the intrinsic quality of the drugs. We thank you for that comment. It is implied. This is really a question, is there a rationale for treating these people.

DR. WOOD: I guess as we go through all of these questions, it is important to sort of keep in mind that perfection is the enemy of the good here. I think that may be even truer in OTC settings than in Rx settings, although much of the data we have

seen speaks to the inadequacy of the Rx efforts as well.

Okay. So, Neal, you are giving a qualified--

DR. BENOWITZ: Yes.

DR. WOOD: Yes; a qualified yes. Keep going.

DR. CAPRIO: I would say yes.

DR. BLASHKE: Yes.

DR. CARPENTER: Yes.

DR. PARKER: Yes.

DR. FOLLMAN: Yes.

DR. PATTEN: Yes.

DR. McCLUNG: Most patients in that group deserve therapy.

DR. WOOD: Sorry; say that again? I am not sure we got that.

DR. McCLUNG: In the target group, there is a range of risk. Overall, the average risk in this population merits therapy but there are patients in this target group whose risk is relatively low compared to the others in the group

and it is not convincing that either, from a risk:benefit ratio, or, certainly, from a cost-effectiveness standpoint, that therapy for everyone in this target group merits therapy always.

DR. WOOD: So, pull the lever. Is it yes or no?

DR. McCLUNG: It is yes if you have to be categorical. But there is always--it is not quite so clear.

DR. WOOD: Put him down as maybe. Let's go back to Dr. Davidoff who missed his chance to vote. We will come back to you at the end, Frank.

DR. CLYBURN: Yes.

DR. MAKRIS: Yes.

DR. CLAPP: Yes.

DR. SCHADE: Yes.

DR. TAYLOR: Yes.

DR. SCHAMBELAN: Yes.

DR. WOOD: Yes.

DR. TINETTI: Yes.

DR. WATTS: Yes.

DR. NEILL: Yes.

DR. WIERMAN: Yes.

MR. SCHULTZ: Yes.

DR. FINCHAM: Yes.

DR. SNODGRASS: Yes.

DR. WOOD: Dr. Davidoff?

DR. DAVIDOFF: Yes.

DR. WOOD: So you need to vote. She hasn't got a vote for you.

DR. McCLUNG: Yes.

DR. WOOD: Thank you. So we have 25 yesses and no no's. Remember, you can abstain if you really want to, if people are unsure of what to say.

The second part of this question, then; has the sponsor provided adequate rationale for use of a fixed dose of lovastatin 10 milligrams to lower cholesterol in heart disease in this population. Let's have discussion on that point first.

DR. TINETTI: I think he question is really different if you include or not include the

part in parentheses.

DR. WOOD: I understand that.

DR. TINETTI: And you told us to ignore that.

DR. WOOD: I would like us to do it with and without that part because I think it does--

DR. TINETTI: It is a very different question.

DR. WOOD: I think it significantly alters the question. That is why I wanted to do it both ways first, if that is agreeable to people.

DR. TINETTI: So we are going to vote twice, then?

DR. WOOD: Maybe we should discuss it with and without and see if that helps us. How about that? Mary, do you want to head that off and explain why you think it is--

DR. TINETTI: I think the big difference is whether or not there is enough evidence to suggest that a sizeable proportion of the population will be able to reach this level. The problem is we don't really have those data. The

CUSTOM study is not able to do it and the randomized controlled trials are a very select population. Even they were only for five years.

So the problem is we don't have any information on the second part. It would be a pure guess. But, overall, I think it is a reasonable question and most of us will answer yes to it.

DR. WOOD: The reason I have concerns about it was that it seemed to me to imply that you didn't get benefit unless your LDL was reduced to less than 130 milligrams per deciliter.

DR. ORLOFF: Alastair, I think your point is a good one. Really, what the question--you know, these are questions intended to make sure that no one has a fundamental disagreement with at least it initial part of this approach because, if they do, then it is a non-starter. The first question was should some of these people be treated with a statin. The answer seemed fairly straightforward. The question here is is a 20-milligram dose of lovastatin an effective dose of lovastatin? Is there evidence that you can

reduce heart-disease risk in this population with a 20-milligram dose of lovastatin.

Forget the 130 thing.

DR. WOOD: All right. We have had further clarification. The reason we are doing that is we think people may benefit--just for the record, people may benefit even if they don't get their LDL down to 130.

Dr. Follman?

DR. FOLLMAN: I think the thing in parentheses is clearer to me, will a sufficient proportion be able to reach this LDL. I think the first part speaks to the point I was trying to make yesterday, will it have a benefit compared to what.

So if we compare the fixed dose of statin to people getting nothing, the answer in my mind is absolutely clear, they would get a benefit. The question that is not at all clear in my mind is compared to a prescription world, would there be, in a population basis, a benefit to this.

We don't have evidence of that to my mind. The study that comes closest to this, though it is

imperfect, is the lipid-lowering trial compliance of ALLHAT which showed really no difference between usual care, which is, you get statin when you think you need it, as opposed to a fixed dose of pravastatin.

So, depending on the reference group, I have one or two different answers to this question.

DR. ORLOFF: I think it is reasonable for me now to try to clarify a little more. In an effort not to get bogged down in these, this question is independent of the marketing status of the drug. Is 20 milligrams of lovastatin an effective dose of lovastatin?

DR. WOOD: That is why I deleted the second part.

DR. ORLOFF: I want you to delete the second part.

DR. WOOD: Okay.

DR. SCHAMBELAN: That assumes the patient is adherent to the medication, David?

DR. WOOD: No.

DR. SCHAMBELAN: Or is that just putting

it into this population and seeing how it works in terms of adherence, or are you asking will it reduce heart disease risk if taken in the prescribed amount on a continuous basis. What are you asking us?

DR. WOOD: I would say--

DR. ORLOFF: Is there evidence that this is an effective dose? It is assumed that effectiveness, or at least optimal effectiveness, depends upon adherence to labeling, whether it be a prescription drug or an over-the-counter drug.

DR. WOOD: But, pragmatically, the answer to the question has to be are there clinical-trial data that support that conclusion.

DR. ORLOFF: That is exactly the question.

DR. WOOD: So that presupposes that people took the drug inadequately or adequately. Okay. Any further discussion on this point? All right. Then let's start again and we will start at the opposite end this time with Dr. Snodgrass.

DR. SNODGRASS: I guess I need to ask a little discussion here. The question, I think, is

framed in a way that is not a straightforward answer. It is the fundamental--I think this is just very elementary. It is fundamental therapeutics that you individualize your dose for a patient in the patient-care setting.

But, in a public setting like this, you have got a fixed dose because you can't individual it. You have got a fixed dose. So there was some response but it is not going to be optimal. So I think that is just a distinction here. So, when you see this kind of question, has it provided adequate rationale, I would look at that in one sense, with those words. But if you are saying beyond that, is the question is there really formal prospective randomized clinical-trial data that 20 milligrams is effective across some percent of a population, I think that is maybe a slightly different question.

DR. ORLOFF: That is the question. I apologize for having to partake too much in this conversation. But, irrespective of marketing status, why not phrase it this way. Although you

have not had the length and the breadth of the efficacy and safety data that were presented for lovastatin for its initial approval presented here, I guess it is reasonable to ask you were we asking you whether to approve a 20-milligram dose of lovastatin, say, in addition to a 40 and an 80 and so on, has there evidence been presented in your package and in the presentations that 20 milligrams is an effective dose, or is it an ineffective dose and is something more needed.

DR. WOOD: Okay. Does that help, Dr. Snodgrass?

DR. SNODGRASS: I think it helps somewhat. I think the way I view it is it will be helpful to some percent of the population and that makes it somewhat helpful. So my answer would be, in that context, yes.

DR. WOOD: So perfection is the enemy of the good, again. Okay.

DR. FINCHAM: Yes.

MR. SCHULTZ: Yes.

DR. WIERMAN: Yes.

DR. NEILL: Yes.

DR. WATTS: Yes.

DR. TINETTI: Yes.

DR. WOOD: Yes.

DR. SCHAMBELAN: Yes.

DR. TAYLOR: Yes.

DR. SCHADE: Yes

DR. CLAPP: Yes.

DR. MAKRIS: Yes.

DR. CLYBURN: Yes.

DR. McCLUNG: Yes.

DR. PATTEN: Yes.

DR. DAVIDOFF: Yes.

DR. FOLLMAN: Yes.

DR. PARKER: Yes.

DR. CARPENTER: Yes.

DR. BLASCHKE: Yes.

DR. CAPRIO: Yes.

DR. BENOWITZ: Yes.

DR. WOOLF: Yes.

DR. WOOD: Okay. It is 25 yeses, no no's.

The next question addresses, as the first

question, that starts to address the toxicity of the drug. Question 2 addresses hepatic toxicity. Before we get into going through the individual questions, maybe we should see if there is any discussion on this point first.

Dr. Parker?

DR. PARKER: The only comment I had just related to the fact that the U.K. puts the warning about alcohol use. I understand that they do that because it came up in discussion that that was recommended and so it is there. I just take note of that again, alcohol use is extremely common in our own country and I think we may want to consider whether or not it is clear to someone that liver and alcohol use relate to the same thing on the label.

DR. WOOD: Let me suggest that--I think that is a good point. Let me suggest that we sort of put in a supplemental question in between 4 and 5 that addressed whether there are other issues that we should address in terms of toxicology or whatever that we have not addressed specifically

under these and we will try and capture all of that at that time if there are issues.

Any other discussion? Yes, Dr. Benowitz?

DR. BENOWITZ: I just want a clarification. I probably should have seen this but I know, in the U.K. package insert, there was a description of symptoms of liver disease and a warning, if you develop these symptoms to call your doctor and stop the medicine.

The safety issue here implies that there is some effective warning for OTC. Is that warning the same or is that present in the current proposed label?

DR. WOOD: Well, it seemed to me the question here related to preceding liver disease at first. So, presumably, that would come from a history of liver disease.

DR. BENOWITZ: You are talking about a. I was talking about the whole--I was talking about c., actually.

DR. WOOD: I see. Okay.

DR. BENOWITZ: I was talking about

Question c.

DR. WOOD: Why don't we hold that until we get to that point.

DR. ORLOFF: Let me take a crack at clarification, yet again. This always happens at the question time. You realize that your best intentions fell short with regard to simplicity. Our intent here is really, Question No. 2 is about the proposal for this to be marketed OTC in the absence of either baseline or follow-up liver-function monitoring.

What I would say is, taking into account a., b., and c., not as questions but as issues about undiagnosed liver disease and safety and the extent to which it has been addressed, about hepatic risk specifically in that population and--well, we don't even need to go to c. The question is, what is the level of comfort, or has there been adequate information provided, to go to market OTC without liver-function test baseline assessments or ongoing monitoring.

DR. WOOD: So, would it make it easier if

we just asked, does the committee think that liver-function tests are required before the drug is taken and are required during the drug's administration. I mean, that would get at the question; right? Okay.

Neal, does that help?

DR. BENOWITZ: The only issue about c. is is it safe.

DR. WOOD: Yes; I know.

DR. BENOWITZ: If you get rid of that, I'm fine.

DR. WOOD: Right. So, with Dr. Orloff's permission, we are going to rephrase the question a little bit and say, do we need to have pre-treatment liver-function tests for patients taking 20 milligrams a day of lovastatin over-the-counter.

The following question will be, and maybe this can be answered together, do we need liver-function tests during administration. Is that fair? Okay.

We will start at the other side, again.

First of all, is there discussion on that that we want to have?

DR. CARPENTER: Speaking from the pediatric point of view, one can imagine the situation where, although this is not in the age group approved for over-the-counter use, that pressures may be to have some patients obtain this medication in such a fashion.

Now, that is a specialized class of people in which the data regarding potential hepatic complications with these drugs is, I think, more limited. We have to consider, with the population that we would use, the encounter with an over-the-counter distribution system that it may get neglected to do what we would probably wish to do, given that this is a special population.

DR. WOOD: I guess--you may want to address that. We are reviewing the drug for the indication that is being sought. It is probably unreasonable, unless we see a major safety issue in some other population, to debate its potential safety or not in populations that are wildly

outside the age group or other parameters that are being sought for.

But, you know, I would defer to the FDA if they think that is important discussion to have. I mean, I guess--well, go ahead.

DR. ORLOFF: What I was going to say is, first of all, this drug, I assume, and Merck is going to confirm this in case my memory is failing me, will be marketed not for use in children. That is the first thing.

The second thing is what do we know about the safety of statins in children where I think you are right. The data are limited. There is a limited number of studies in a relatively small number of children with heterozygous familial hypercholesterolemia and, obviously, there is a smattering of children with homozygous FH who have been treated.

In those studies which, all-told, on statins probably count in the several hundreds at most, for up to a year, my recollection of the data is that there is absolutely no liver signal at all.

These are at doses of, I believe, 20 and 40 of lovastatin, torvastatin, 20 milligrams--I don't remember what--simvastatin as well, I believe, 20 milligrams of simvastatin.

But that is all we know. I think the issue of pediatrics came up yesterday and I apologize we didn't get to it in response to that question yesterday.

DR. WOOD: Dr. Follman?

DR. FOLLMAN: I just wanted to--the question talks about the evidence that the sponsor has provided. I think it is important to know that we are talking about baseline liver-function tests and undiagnosed liver disease. Liver-function testing is a requirement or in the label for prescription statin and so all the evidence that we have about the safety of statins in terms of liver problems is in this population that presumably doesn't have liver problems at baseline.

So, if we look for data or evidence for this select group, there was one small study that was done. It is a retrospective study that the

sponsor mentioned where there are about 340 people with elevated liver enzymes who were looked at prospectively with a statin compared to a group with elevated enzymes who didn't get a statin and they showed no real difference there.

So I wanted to just reinforce the point that we have a huge body of evidence on the safety of statins in terms of this for the screened population and we don't have that much evidence, this was one study and another very small study, regarding the issue whether they should be checked at baseline for liver abnormalities.

DR. WOOD: Does the sponsor want to respond to that question in any way?

DR. WATKINS: Paul Watkins, University of North Carolina. I really don't have any additional comments other than was made yesterday. As you saw, some preliminary data of a much larger study that is ongoing at Kaiser, the final results and analysis will be forthcoming.

But the only point I made then is that we know in the 27 million patient years a significant

proportion of those will have had fatty liver and, undoubtedly, viral hepatitis. In spite of that, we all know the remarkable safety record from a liver standpoint.

So the incremental risk in people with preexisting liver disease, if it exists, has to be very small. The overall risk has to be small in that population.

DR. WOOD: Dr. Wood, may I just make a comment here. I hope this will be useful to the committee members. Yesterday, Dr. Hemwall had actually mentioned that the sponsor has already submitted to the agency a supplement to make changes to the label with respect to LFT, and, actually, it is LFT recommendations, not requirements, in the label.

While we can't comment on an application that is still under review, certainly the sponsor is open to discussing what they are proposing. I would want to share with the committee what has occurred with other statin labels. Over the past five to six years, we have received applications

requesting changes to the label to pretty much ease up on the requirement of LFT monitoring.

The data submitted are based on large controlled clinical-trial data. I think it is reasonable to say that, if similar data are submitted to the agency for Mevacor, we would be hard-pressed not to grant them similar changes to their label. Similarly, as the sponsor has alluded to, there are preliminary data that we have not reviewed and we have encouraged them to submit it to us because we do feel that, given the weight of evidence of the safety of this product with respect to liver toxicity, this would be very useful information for us to review and possibly change the label based on those data.

DR. WOOD: Okay. That is very helpful.

Dr. Davidoff?

DR. DAVIDOFF: Not having gone into the evidence with the kind of thoroughness that might be involved in doing, say, a Cochran systematic review, the data that I have seen are not persuasive to me that there is any significant

risk.

That makes me also raise the question about the wise use of healthcare resources. I mean, everybody knows that, in this country, we are spending vast amounts of resources on healthcare. I am not just talking about cost here. I am talking about people and time and equipment and supplies and money.

If liver-function tests are really, in the clinical sense, not necessary, it seems to me it is worth considering whether requiring an ineffective use of healthcare resources which are getting increasingly precious is something that we should take into consideration. It is not just a matter of cost in the strict financial sense.

DR. WOOD: So, Dr. Parks, you have been told to hurry up.

Dr. Taylor?

DR. TAYLOR: Actually, my questions were mostly answered. It was a regulatory question about the requirement of having LFTs since it was not required but recommended for the prescription

label.

But I would, I think, like to see--I would like to see a stronger label in regard to liver disease and alcohol in particular, similar to the Zocor label. I think the current label, as we have reviewed, is not sufficiently strong.

DR. WOOD: Let's hold that thought because I will give you the chance to offer that later.

Any other discussion, then? Then let's move, I guess, to the rephrased questions which, if I can remember them again, are, do we think that liver-function tests are required prior to starting lovastatin therapy and, as a supplement to that, do we think that liver-function tests are required at some regular basis during therapy to ensure the continued safety of the drug, something like that. Is that okay?

DR. ORLOFF: I just remind people, again. Dr. Parks mentioned the Kaiser study that the sponsor presented in brief yesterday had not been reviewed. But the issues are two. One is, is there sufficient evidence of the safety in patients

who have existing liver disease and is there sufficient evidence, presumably because the evidence we have now is--the vast majority of the exposures in trials are in patients who don't have baseline liver disease. That, on top of whatever other information is brought to bear, is there enough information there to support safety in long-term use without follow-up monitoring.

DR. WOOD: And then the unspoken assumption which I am not sure we know either, is that measuring liver-function tests and finding them to be abnormal would actually protect that patient from some further damage which is not a--so that is an important consideration before, as Frank says, we advocate a test.

Let's start again, then, with Dr. Woolf. Are people comfortable doing both of these at once? Okay. Let's do that.

DR. WOOLF: I do not think that we need to require LFTs before or during. The answer is no.

DR. WOOD: So the answer is no. The way we are asking the question is if you don't think we

should do it, then the answer will be no.

DR. BENOWITZ: No, no.

DR. CAPRIO: No, no.

DR. BLASCHKE: No, no.

DR. CARPENTER: No, no.

DR. PARKER: No, no.

DR. FOLLMAN: No, no.

DR. DAVIDOFF: No and no.

DR. PATTEN: No and no.

DR. McCLUNG: I agree with no and no.

DR. CLYBURN: No and no.

DR. MAKRIS: No and no.

DR. CLAPP: No, no.

DR. SCHADE: No for both.

DR. TAYLOR: No for both.

DR. SCHAMBELAN: No for both.

DR. WOOD: No and no.

DR. TINETTI: No and no.

DR. WATTS: No and no.

DR. NEILL: No, no.

DR. WIERMAN: No and no.

MR. SCHULTZ: No and no.

DR. FINCHAM: No to both questions.

DR. SNODGRASS: No and no.

DR. WOOD: So, obviously, everybody voted

no. The next question relates to another toxic problem from statins which has been in clinical trials more common, I guess, serious muscle toxicity The question says; 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 25 milligrams acceptable for an OTC drug?

Do we have any discussion on this point?

DR. WATTS: I think this question raises the issue of whether or not patients can appropriately self-select. I think, for patients who stand to benefit--that is, those who are at moderate to moderately high risk, then the muscle effect, I think, is reasonably safe.

But for patients who don't stand to benefit, I think the muscle concern is not

acceptable. That is discussion. That is not a yes or no answer.

DR. WOOD: No; I realize that. So, for patients who don't stand to benefit, who are the--

DR. WATTS: I can extend it into an answer, if you like, and that is that, given the problems that I see with self-select, that, overall, for the population who self-selects, I don't think it is safe.

DR. WOOD: Okay. Any other discussion? Mary?

DR. TINETTI: I just had a question and maybe it came up yesterday but I missed it is probably the drug that most likely is going to be used by this population is erythromycin. We use it fairly frequently. Do we have any evidence for the short-term use that people are using erythromycin with the 20 milligrams. Is there any evidence of an concern with that combination?

DR. HEMWALL: The best evidence comes from a slide we showed in our core presentation yesterday when the time was, before we knew about

the CYP 3A4 interaction, there were people in AFCAPS that were actually coadministering interacting drugs. If one of you knows that core slide, you can bring it up right now. Otherwise, I will give you the number.

[Slide.]

These are the most potent of the CYP 3A4 inhibitors. In this case, there were over 500 patients randomized to lovastatin 20 to 40 milligrams that were given these strong CYP-3A4-interacting drugs. This included erythromycin and clarithromycin but the other two there, the ketoconozole, nitraconazole and only one or two on nefazodone. The point of the two azoles, they are even more potent than erythromycin and clarithromycin.

So you have got a group of 500 people receiving these drugs and their risk of having a musculoskeletal side effect is very similar to that seen with the placebo group receiving the same drug.

So what we are saying here is that the

label is very strong about checking with your pharmacist or doctor if you have a new prescription or you are already taking medication. But if someone slips through and is taking a medication, then the absolute risk is still very, very small even though the relative risk may be increased.

DR. WOOD: While you are answering that, I guess the signal with Baycol was first evident with the interactions with an elevation in CK. So, do we know if the 48 or whatever it was that was up there on the top line of that slide, what proportion of these had an elevation in CK as the reason for being there and how high did the CK, CPKs, go?

DR. HEMWALL: We don't have that readily available.

DR. WOOD: Okay. If you come up with that, let's get back to that later. The other question is do we know what the increased C and AUC is with erythromycin, with lovastatin. Well, we do, but why don't we quote it.

DR. HEMWALL: Using the enzymatic assay, I

believe it is around four- to five-fold.

DR. WOOD: So that would take you from a dose of 20 milligrams up to a dose of 80 milligrams.

DR. HEMWALL: In a very strict sense, it would. But there is a lot more kinetics around it than just--

DR. WOOD: Understood. How strong is the dose-response relationship of muscle toxicity?

DR. HEMWALL: There is a dose-response relationship that increases but it is still rare at the high dose of lovastatin.

DR. WOOD: Dr. Carpenter?

DR. CARPENTER: Should we consider this question for our target population, for the target population, as opposed to overall because we deal with selection issues with later questions.

DR. WOOD: That is a helpful comment. Yes.

DR. BLASCHKE: I just had a question about this last slide before you sit down. I was unclear what the placebo population was taking there in

that slide.

DR. HEMWALL: In order to match the groups, the placebo group was also taking the same interacting drugs, but not lovastatin.

DR. WOOD: Dr. Davidoff?

DR. DAVIDOFF: I seem to recall that there has been concern with other statins with their interaction with fibrates in producing muscle damage. Am I mistaken and, if I am correct, is there any information on the interaction of this dose of lovastatin and fibrates?

DR. WOOD: The gemfibrozil story with Baycol was particularly because of the multiple pathways that were inhibited by gemfibrozil with Baycol which made it particularly susceptible to that. This is a drug metabolized by 3A, so it wouldn't be as susceptible as the others. But the sponsor should answer that question, I guess.

DR. HEMWALL: All lipid-lowering drugs are associated with muscle side effects. If you combine two lipid-lowering drugs, you get increased rates of muscle side effects. In the case of

cerivatstatin, there was a particular interaction with a metabolic pathway that was exacerbating that effect that is not seen with lovastatin.

DR. ORLOFF: I am sure Merck has more precise numbers but let me just add a little bit and say that the pharmacokinetic interaction with cerivastatin, between gemfibrozil and cerivastatin--that is to say, impacting systemic exposures to cerivastatin was marked compared to lova. So, as Dr. Hemwall has said, something like five-fold increase--

DR. WOOD: Eight-fold.

DR. ORLOFF: Eight-fold increase of cerivatstatin with only a two- to three-fold increase in lovastatin. It is believed, and I think the sponsor would agree here that it is not--the precise nature of the interaction between gemfiboizil, specifically, and lovastatin, specifically, to augment the risk of myopathy is not fully understood. But, in all likelihood, it is both a tissue site--that is to say, at the muscle, pharmacodynamic interaction but also,

perhaps, to some extent, a pharmacokinetic interaction whereby gemfibrozil increases the risk of myopathy from lovastatin, per se.

DR. DAVIDOFF: That is helpful, but all that said, what are the clinical data on the occurrence of rhabdomyolysis with that drug combination. That was my question.

DR. WOOD: Do you want to respond?

DR. HEMWALL: Do you have some information on that? We can get that for you, if you want it. But I guess one of the more relevant comments would also be that someone taking a fibrate is most likely to be under the care of a physician managing their lipids and would not likely also take an OTC statin on top of that.

DR. LEVINE: I have the data from our postmarketing database. Of the 336 reports of rhabdomyolysis, there were 97 reports which included fibrates. 96 of them were gemfibrozil. Of the ones that we know the doses, 16 were at the 20 milligrams, out of the 97.

DR. WOOD: Dr. Taylor?

DR. TAYLOR: I wanted to be reminded of the muscle-toxicity data from the CUSTOM study and the other question is I don't think we ever saw

data on the average number of medications that individuals of the CUSTOM study, the users, were on. I would like to know that.

DR. HEMWALL: It will take a couple of seconds here. We will get a slide.

DR. WOOD: Why don't we work on that and we will come back to you on both these questions.

Any other discussion? Dr. Benowitz?

DR. BENOWITZ: I am sure this is going to be a small population, but I looked at the label and I didn't see any way to warn the user--that is people with transplants getting cyclosporine which is obviously a question. I don't see an exclusion for such a person there except if you had a heart transplant. But a kidney transplant person, there would be nothing on the box that says, "Don't take it."

I was wondering how a patient is supposed to know about the cyclosporine issue which has also

been associated with interactions.

DR. WOOD: Given the risks from a transplant with atherosclerotic disease. I think most of these patients will be on a statin.

DR. BENOWITZ: Probably. I don't know. That might be the case.

DR. LEVINE: From our CUSTOM study, as you recall, there was no myopathy reports and no rhabdo reports. We did not measure CPK in that study. There were 118 participants which is 11 percent which reported myalgia as an AE. 79 were considered drug-related and 39 were not considered drug-related.

DR. HEMWALL: I think Bob has a concomitant medications number. A couple of things on the labeling, or course. Number one, there is a lot of labeling reminding people to watch out for myalgia. If you look at some of the packaging, you will see the icon of the muscle pain, et cetera. So this is something people are very much alerted to.

On the question of cardiac-transplant

patients and cyclosporine, the internal package materials also actually specify the drug cyclosporine. But, more importantly, on the very back panel, again, as we talked about yesterday, people who have heart disease and I would think cardiac transplant would fall into that category and the consumer would know that or not to take that drug. So that would, hopefully, eliminate those folks.

DR. WOOD: Of course, I don't think Neal is just asking about heart transplants. But I have made a note that there is a list of exclusions we are hearing about that maybe should be in the label. We have heard about one from Dr. Parker and from others. Maybe we should sort of collect them. In this subsequent question, we are going to ask between four and five--not 4:00 and 5:00 p.m., unless people--

MR. TIPPING: So the question about the average number of medications, I think it was, that people were on in CUSTOM. Again, because of CUSTOM being a naturalistic behavioral study, we didn't

collect concomitant or prior therapy information to the degree that you might expect in a traditional clinical trial. Instead, we asked specific questions, were you on lipid-lowering therapy, were you on an interactive medication, things like that.

So we do have information on lipid-lowering therapy. I think the most important thing you are asking about is the interactive meds.

DR. TAYLOR: Right. Specifically. But I wanted to also get back to this issue of whether the CUSTOM population represented the general population because, in that age group, I would think that--the number of medications might be a marker for the population. If you have the same rate of additional medications, that would give credence that you were dealing with the same population.

MR. TIPPING: I think we have information on the number of individuals--the number of evaluators in CUSTOM that were on any prescription medication. Can you find that number for me? I need a pair of glasses for this one. There were

630 of our 3,316 evaluators who were on any prescription medication.

DR. TAYLOR: 630 out of how many?

MR. TIPPING: 630 of our evaluators--so it is out of 3,316.

DR. WOOD: How many of these went on to elect to take it? I guess that is the question. What is the proportion in that group?

DR. TAYLOR: I guess my point is that if you ended up with a group that none of them were on other medications, that wouldn't look like the real world. I guess that is my point.

MR. TIPPING: Let me go back and take a closer look at this table.

DR. WOOD: Okay. Any other discussion on this point? Then let's move to the question. Statins have been associated with the development of serious muscle toxicity. Further more, drug-drug interactions with lovastatin may increase the risk of muscle toxicity. Is the risk of muscle toxicity with lovastatin acceptable for an OTC medicine?

I am going to start with Dr. Snodgrass--I'm sorry?

DR. WIERMAN: Somebody has asked you to

limit that to the targeted population because we are going to come back to the ability to self-select. Are you talking about--

DR. WOOD: Well, I guess--help me. Explain.

DR. McCLUNG: Let's confine it to the target population. I think, for the purpose of discussion about the muscle symptoms, that would be a cleaner thing, and then deal with the capacity of patients to self-select as a separate question.

DR. WOOD: Okay. That's a good thought.

Dr. Snodgrass?

DR. SNODGRASS: Yes.

DR. FINCHAM: I hate to do this but what is the targeted population? Is it anybody that can purchase the product? Now, just let me--is it anybody that can purchase the product or is it those that select to use the product based upon reading the label.

DR. WOOD: Or a third question is is it those who select it correctly. I think, and I don't want to put words in your mouth, but you were talking about the population that was on the label. Am I correct?

DR. FINCHAM: Yes.

DR. WOOD: Okay.

MR. SCHULTZ: Yes.

DR. WIERMAN: Yes.

DR. NEILL: Yes.

DR. WATTS: Yes.

DR. TINETTI: Yes.

DR. WOOD: Yes.

DR. SCHAMBELAN: Yes.

DR. TAYLOR: Yes.

DR. SCHADE: Yes

DR. CLAPP: Yes.

DR. MAKRIS: Yes.

DR. CLYBURN: Yes.

DR. McCLUNG: Yes.

DR. PATTEN: Yes.

DR. DAVIDOFF: Yes.

DR. FOLLMAN: Yes.

DR. PARKER: Yes.

DR. CARPENTER: Yes.

DR. BLASCHKE: Yes.

DR. CAPRIO: Yes.

DR. BENOWITZ: Yes.

DR. WOOLF: Yes.

DR. WOOD: So everybody voted yes.

The next question relates to pregnancy,

Category X. Before we sort of get into that question, it seemed to me that the FDA ought to consider--have symbol that they put on packages that says, "Not to be taken by potentially pregnant women," sort of INTEL inside that was popularized, and that that would provide us with a lot more reassurance if there was some kind of--and I am not smart enough to work out how to do that, but we should think about that.

Bob?

DR. MEYER: There is actually, just to directly respond to that, some interesting data about use of symbols, though. For instance, there

was once a silhouette of an obviously gravid woman with the universal "no" sign above it. Lots of people who looked at that then thought that that medicine was actually a contraceptive. So you have to be careful with those kind of considerations.

DR. WOOD: That reflects on the quality of the symbol, I guess. But at least they thought something; right? This is obviously an issue we are going to have to think about.

So, let me read the question to you; lovastatin and other statins are currently labeled as Pregnancy Category X, the drug should not be used during pregnancy. We have had a lot of discussion that I would like not to repeat, if we can avoid it, that talked about how one gets to be a Category X product. You can get there either from proven pregnancy toxicity or lack of efficacy during pregnancy. Either of these will put you into that category.

The company's position here, I guess, and others is that this is no efficacy--there is no requirement for this drug to be given during

pregnancy and no demonstrated behavior during pregnancy and, therefore, that would make it Category X.

The second part of the sentence is; Has the spectrum and magnitude of fetal toxicity with lovastatin 20 milligrams been adequately studied, obviously an important question. Is the risk for women of childbearing potential appropriate for an OTC product?

It seems to me that we are going to have to discuss, either here or later, is the adequacy of the self-selection or self-exclusion appropriate and are there ways to strengthen that.

So let's set off. Any discussion on this topic? Dr. Woolf?

DR. WOOLF: I would like to come back to the issue that was tabled before. We were told that there are roughly 5 million people who are a target for the drug. From the CUSTOM study, there were roughly 5 percent of women who were age 40 to 45 and another 5 percent who were 45 to 50.

Since I have raised the issue and a member

of the audience was kind enough to give me the pregnancy rates for these individuals, and it is 4 per 1000 per year in the 40- to 45-year age group and a fifth of that, or 1 per 1000 per year, in the 45 to 49.

Assuming my algebra is correct and I am not sure that it is, that leads to roughly 15,000 women per year who potentially could be taking this drug not according to label but were in the CUSTOM study. I would submit that the people in the CUSTOM study probably do not represent the usual consumer but somebody who are self-selected to participate in the study. So there are roughly 15,000 people per year who will get pregnant while taking the drug.

We were given some data this morning about teratogenicity that we did not have yesterday that suggests that there might be a class effect. That has me concerned. With 15,000 women exposed and even a few percent of them have an affected baby, that is, to me, a big deal.

DR. WOOD: Any other--yes.

DR. WIERMAN: The only comment I would make is your statistics assume, in that group between 40 and 55, that they are not using any

forms of contraceptive.

DR. WOOLF: Absolutely. So that is the upper bound. But it is per year, so it is a cumulative exposure.

DR. WiERMAN: Absolutely. My only comment on that, although I think it is an important to discuss related to the pregnancy issue, that cholesterol treatment in this highly motivated group of patients that are seeking healthy lifestyles, the data has repeatedly shown us that women, especially premenopausal women, are not focused on treating their cholesterol and, in fact, it is hard to motivate post-menopausal women to treat their cholesterol.

So the absolute risk versus the potential theoretical risk for this adverse outcome, I think we continually need to use data and not just emotional responses to.

DR. HEMWALL: I would like to add, to put

that in perspective. The information I showed the committee yesterday was to try to add what you might consider the incremental risk calculation. There are about 400,000 women per year, or at least, shall we say, 400,000 prescriptions written per year today for statins for women of childbearing potential.

So we are talking about what may be the incremental risk that you are concerned about, but there is already this level of exposure going on, admittedly under a physician's care but I think that level of incremental risk is not greater than the overall risk that we are already seeing.

DR. WOOD: Any other discussion?

DR. CLAPP: Just as he mentioned that there are prescriptions written, 400,000 a year, for women who are not in the age category that are the targeted population, I think we have to have concerns for the effects of direct marketing. Although it is speculative for sure, we know that the direct marketing will affect women who, perhaps, have heard or it is registered that their

cholesterol is elevated and then, perhaps, rather than seek medical treatment or change their diet or exercise, purely speculative, as human nature would lend some to do, would see the Mevacor and think that this is an opportunity to make a change that is in their health's best interest.

I can see an opportunity for many women, black women, in particular, who, perhaps, do not have the opportunity or the resources to have ongoing medical care, accessing Mevacor because they have been told at some point, because screening for cholesterol officially starts at 20, that their cholesterol is elevated and, perhaps, not focusing in on the guidelines thinking that they are doing something that is heart-healthy for themselves, maybe putting themselves at increased risk for this adverse outcome.

Although the data is unclear, there is some concern. As the Merck scientist said yesterday, reasonable scientists can come to different conclusions. That is my concern with the information about the potential congenital

malformations of the fetus or newborn child.

Additionally, the marketing of the medication is concerning. I am looking at, and I should have raised this yesterday, admittedly, I am looking at some of the pamphlets included in the package insert. They have a picture of a black woman hugging a gentleman. I am not sure who the target is here. I have been asking my colleagues how old she is and some say over 55. Some say under 55. But she looks like a lot of black women who are not 55.

So I am not sure if she is hugging the recipient of the Mevacor or if there is a subliminal suggestion that she, herself, could be a candidate for Mevacor because there is a sidebar here and I am not sure what it is.

So we have her in closeup in other one, but I am still unsure of her age.

DR. NEILL: She looks younger than 55 because she is tasking Mevacor.

DR. CLAPP: There you have it. We all should take it for that reason. But, nonetheless,

I think I am concerned because we haven't seen the phenomenon of direct marketing. The outcome that people who, perhaps, are indigent but want to improve their health and don't have the resources but might want to take a pill. They don't diet. They don't exercise.

I am skeptical--I know that it not the targeted group, but I am concerned. As we know, at least 50 percent of pregnancies are unplanned so the cautions about pregnancy and lactation are interesting but, if you didn't plan on becoming pregnant, you are taking the medication and the warning is too late for you.

DR. WOOD: Any other comments? This is obviously an important issue. Dr. Patten?

DR. PATTEN: I share Dr. Clapp's concerns and I have some questions in that regard. We have animal-model data that indicates that statins can be a factor in birth defects. We had a presentation earlier regarding human consequences and we have prevalence figures here, 1 in 10,000 for very serious defects.

I have a question for the FDA. The way the question to us is going to be stated is, is the risk for women of childbearing potential

appropriate for an OTC drug product. I would like to know what you consider appropriate and I would like to have this question answered with regard to some other OTC drugs so I have a basis for comparison here.

DR. WOOD: Okay guys, does that put you on the spot?

DR. BULL: I think one thing, if we lived in an ideal world, that should be kept in mind is that the ideal targeted population, if the product were to be used the way that it is supposedly being indicated, which would be women who are postmenopausal who would not be in their childbearing years, you probably don't have the problem we have.

Yesterday, the example of Accutane came up. One of the reasons Accutane's risk management is so critical is that indicated population is also the population at risk for its indication for use.

So I would encourage you to keep in mind the way that the drug--the target population, I think, is certainly a critical one, but you also have data that you are going to have to weigh as to what happens in actual use.

DR. WOOD: But you are not--just to make sure we all understand this. You don't mean to imply that you think this is like Accutane, do you?

DR. BULL: Oh, no; not at all. But I wanted to make that clarification because one of the issues we struggle with with Accutane is that the population, which is women of childbearing potential, is also the population that has acne.

DR. WOOD: But I think the question that we are being asked is--not to let you off the hook--is you are asking us to decide whether it is appropriate. I think you were being asked what you think based on your previous experience, your historical experience, your whatever is appropriate, number one. Number two, I suppose, in order to be able to answer that, what is your assessment of the risk of pregnant women of this

product right now. Is that fair, Dr. Patten? Is that what we are trying to--

DR. PATTEN: Yes.

DR. BULL: I feel as if you all are flipping the question back to us which is why we have convened you all here.

DR. WOOD: We are.

DR. BULL: I think one element to keep in mind is that we have data from the actual-use study that I think needs your input and evaluation because the packaging, the label that was submitted, certainly provided guidance to the consumer as to--that had age guidelines. And you have data that appears to be at variance with that. I think that that is the open question.

I don't know if others from FDA want to comment at this point.

DR. WOOD: I don't see a rush.

DR. TAYLOR: To follow up on some of this discussion, I think it is presumptive to think that the target population is going to be the population that you think it is. Even in your own data, you

say that 37 percent of women users were less than 55 in the CUSTOM study. So I think it was mass marketing. You are likely to get a great number of individuals who are below 55 and maybe in some reproductive range.

In terms of populations, in terms of populations with elevated cholesterols and LDLs, the population that I see--we start treating that much earlier, perhaps, than another population. It is not accomplished, generally, by lifestyle changes or other changes, strong genetic penetrance of elevated cholesterol.

So I could see a number of individuals in the reproductive range going out and buying this medication which would put them at risk.

DR. HEMWALL: I just thought it would be helpful to put the question in perspective as Dr. Clapp had asked. There are OTC drugs that have significant teratogenicity potential. The most important ones, of course, are the nicotine-replacement products where the benefit to have the population have easy access to

smoking-cessation products is seen to outweigh the potential that women may inadvertently be exposed.

I think we can adopt some of the labeling that has been used for those products to really make it very clear that, if you are of childbearing potential and/or considering having a child, trying to have a child, that you should stay away from these products.

Similarly, there are animal data for many OTC products that show similar profiles, if not worse, at least in the way animal data are interpreted in terms of the exposures.

Do I have the slide on that? I could give you some information.

[Slide.]

I apologize. It is a little hard to see. But there are actually three OTCs here, cimetidine, epinephrine and ibuprofen. You look at the effect level, milligrams per kilogram and the dose ratio to humans--excuse me; I am getting multiple pointers handed to me. For cimetidine, milligram-per-kilogram effect level, that is a 9.2

human ratio. Epinephrine, which is used in asthma preparations, 0.78. Ibuprofen, which is commonly used obviously has animal ratios that are even below those of the human exposure. This is, by no means, meant to imply that these drugs are unsafe but this is the type of information that you see in animal studies and it is the kind of factoring that goes in in terms of benefit:risk.

The interpretation of the animal studies and relevance to human exposures, these drugs are still viewed as safe and, of course, do not have adverse pregnancy outcomes above the norm in their background. The exposure levels in lovastatin are, indeed, higher than any of the these. Of course, as we said, there may be some argument about what the exposure levels are, but these, we believe, are the appropriate ones and we think that we are very much in range with what is acceptable for an over-the-counter drug.

DR. WOOD: Dr. Clapp.

DR. CLAPP: I think that slide--I was intrigued by the slide yesterday because I think

there is such a vast difference in comparing those medications to Mevacor. For one thing, the cimetidine, even if you find the anal-genital distances a little wider or smaller, I don't think it is comparable to holopresencephaly for some of the skeletal defects that are suggested, perhaps not proven but associated--or there is an alleged or concern of an association between this medication and that specific birth defect.

DR. HEMWALL: Yes.

DR. CLAPP: I am sure there is a lot of distance for argument and for more information but I don't think it is comparable. Secondly, epinephrine--do you mean epinephrine that is used for resuscitation for those who are in status asthmaticus?

DR. HEMWALL: It is ephedrine.

DR. CLAPP: Is medication that is used by a physician. It is not over-the-counter. So it is something that is used at the discretion of a physician administering it to a patient which is not comparable to a patient buying an

over-the-counter medication.

The ibuprofen and fetal-duct constriction, as I recall, happens during the third trimester of pregnancy if there is an exposure to ibuprofen, the duct anomalies. Ibuprofen; it is over-the-counter but, perhaps--there is no warning on it but, as I recall, that is a third-trimester exposure that might be associated.

DR. HEMWALL: You are absolutely correct.

DR. CLAPP: So that is the difference between something that, perhaps, there is an association made but not proven in the first month or two of pregnancy when a women would not be aware of the pregnancy.

But, for a women who is taking over-the-counter ibuprofen, she knows that she is six-months pregnant by that time. Finofibrate, I have no knowledge about that.

DR. HEMWALL: That is just a comparison of a another lipid-lowering drug.

DR. CLAPP: Is that an over-the-counter medication? I don't think so. So there is a

difference. Even though those are Category C--

DR. HEMWALL: Correct.

DR. CLAPP: The outcomes are different and the method of obtaining them is vastly different than that--

DR. HEMWALL: I agree with you on all those points. The point I was trying to make is that animal data can be found in a whole wide range of drugs and most of the drugs are normally classified Category C because there is actually a benefit to use those drugs. You could see the same thing in drugs for asthma or diabetes.

If we then just look at the clinical data, which you saw another presentation of the same clinical data that was presented yesterday in the Open Public Session today, the FDA has reviewed those data and the quote that the Office of Drug Safety put in their review was that a causal association between in-utero statin exposure and identified birth defects cannot be made based on this information.

So I want everyone to just try to put this

all into perspective of what the actual risk may be, given the fact that half a million women in the prescription setting are being prescribed statins every year of childbearing potential, that there may be an incremental increase in that number with the OTC availability and we are very committed to minimizing and making sure that those women that could be come pregnant get a much, much stronger label message than is currently in the label as we have proposed today.

We are willing to work with FDA along those lines.

DR. WOOD: Let's make sure the sponsor has a chance to respond to these questions. Are there questions from the committee that they want to put directly to the sponsor about this specific issue? Dr. Makris?

DR. MAKRIS: I just think that it is very difficult to try and estimate what the risk actually is because there really are some uncertainties. Some were brought out this morning that the human incidence data may actually be an

indicator or some birth defects.

In addition, in the animal data, there are indications of behavioral alterations in offspring that I don't think have been explored adequately to determine whether or not these effects, in fact, are attributable to early gestation exposures in the animals or if they are relevant to humans.

Certainly, that is a type of birth defect, a type of developmental anomaly as a functional effect. So I think that these things have not been adequately explored and probably need some additional study. But it also prohibits us from really getting a good handle on what the risk is. I think that discussion about fortifying the label is really appropriate in this situation.

DR. WOOD: Are there other questions that we can put directly to--Frank, do you want to put yours directly to the sponsor?

DR. DAVIDOFF: This is really more by way of a comment on the very interesting data that close to a half a million prescriptions are being written for women in reproductive years for

statins, or perhaps it was particularly for lovastatin, because I think the point here, or there, is that those prescriptions are almost certainly being written for women who are at really quite high risk, high enough, of cardiovascular events to warrant prescriptions for statin drugs.

Here we are dealing with a matter of benefits being weighed relative to risks. Since, as I hope to be able to talk more about this later, I think the presumed benefits from the targeted group for OTC lovastatin are at least an order of magnitude, perhaps more, less per unit of population than they are in the prescription setting.

I think that shifts the benefit:risk ratio here. So, even if the risk is really quite small, as I am sure it is, for bad fetal outcomes or pregnancy outcomes from lovastatin, I think that you can't really extrapolate from those 400,000 or 500,000 prescriptions and the benefits that might be expected from those relative to the risks for an adverse pregnancy to the over-the-counter situation

where I think the balance of benefits and risks is going to be very different.

DR. WOOD: Any other--Dr. Fincham?

DR. FINCHAM: Just a comment. In my own mind, I cannot make the analogy between nicotine-replacement-product labeling and what the issue is with lovastatin in that pregnant women who smoke are at risk, period, and they use nicotine-replacement products. Is it less safe? More safe? I don't know.

The only analogy I can see with lovastatin is perhaps is somebody is using an herbal product imported from the east that may have some of the drug in it. So, in my mind, I would encourage us not to talk about nicotine-replacement products in this context. That is just an opinion..

DR. WOOD: Dr. Taylor?

DR. TAYLOR: Again, just a comment. Lovastatin remains a Class X; is that correct?

DR. WOOD: Right.

DR. TAYLOR: I don't think we need to forget that. Secondly, the medications that were

on the slide were mostly intermittently used medications for symptoms whereas this medication is proposed for chronic use over years. So I think we have to factor that into whatever decision we make relative to risk.

DR. WOOD: Dr. Carpenter?

DR. CARPENTER: Just a comment amplifying Dr. Clapp's appreciated comments. There seems to be a little concern of a mixed message that may come through when looking at the label and listening to the nature of the way, perhaps, we heard this morning from the consumer groups, the way this medication is already being perceived and may be advertised in the future, and that is as a more natural, more wholesome product.

I am concerned that, particularly in this pregnancy setting, when the big picture and the advertising and television and the color photos in the store are going to convey this message and the label is going to mention, don't take it if you are pregnant, that the latter may get a much lesser play.

I would challenge that the sponsor needs to not only consider the label but consider the nature of that kind of advertising approach,

although FDA, I know, has little to do with that. But has there been any consideration in terms of how to work out a theme regarding this issue given the nature of the mixed message that you can sort of see at present in this regard?

DR. WOOD: Okay. Here is what I propose we do. I think this is obviously a very important issue and I don't want to, in any way, short-change it. So I think what we could do is to take our lunch break now, return at 12:45, make sure we complete our discussion at that time and then take a vote. That will also allow the sponsor to give any thought that they want to make any responses after that.

I had hoped we would finish before lunch, but that is out of the question. So we will be back at 12:45 and start promptly.

[Whereupon, at 12:00 p.m., the proceedings were recessed to be resumed at 12:45 p.m.]

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

[12:45 p.m.]

DR. WOOD: All the committee seem to be back but we seem to be missing the FDA staff. Is that right? We have all the committee?

As you remember, we left this issue, the pregnancy issue. When we were broken, I tried to reformulate the questions a little bit and see if this works for people. I made the first question, have you heard data that suggest to you that this drug is so potentially toxic to the fetus to prevent it ever being marketed OTC under any circumstances. So, disregarding all the other stuff about labeling and all these sorts of questions first, within the context of what we think about with any drug, and the relatively very limited number of reports of any toxicity here, whether anyone really thinks that is the case.

The second question was going to be is the proposed labeling adequate to exclude women of childbearing potential from taking this drug based on the CUSTOM study or whatever other data we have

seen. If the answer to that is either yes, obviously, or no, and, if it is not, what would you want to see that would be adequate to get you to the stage that that would be appropriate?

Does that sound helpful to the committee? So let's proceed on that basis and let's discuss the first question which I will repeat for everybody's benefit. Have you heard data that suggest to you that this drug is so potentially toxic to the fetus to prevent it ever being marketed OTC under any circumstances.

So, ignoring the quality of the labeling studies, ignoring all that stuff for the moment, just looking at the biology, if you will, what do you think?

Now, do we want to have some discussion on that first? Yes, Frank?

DR. DAVIDOFF: I appreciate your reformulating that first question, but you have put it in extraordinarily absolutist terms. I mean, it is hard to vote on something ever being available, et cetera, et cetera.

DR. WOOD: You are an editor, too. Give me some--

DR. DAVIDOFF: I think it is just asking

for a kind of judgment that is very--

DR. WOOD: All right. We will soften it a bit. But you get the sense, anyway. I meant it to take an extreme position and then we can move back from there. Can we have some discussion on that first? No? Are we ready to vote on that? Then let's take a vote on that.

DR. FINCHAM: Alastair, I am not sure everybody was in the room when they heard your reformulated questions. I was, but--

DR. WOOD: Then let me reread them again with Frank Davidoff's proviso. My question is; have you heard data that suggest to you that this drug is so potentially toxic to the fetus to prevent it ever being marketed OTC. I said, "under any circumstances," to remove from this discussion labeling issues and all the other kind of issues that we are going to get to under the second question.

The second question was; is the proposed labeling adequate to exclude women of childbearing potential from taking this drug based on the CUSTOM study or whatever else you have seen. A sub of that is, if your answer to that was no, what would you want to see that would be adequate?

So let's start with Neal Benowitz. The question is--let me make sure we understand which way we are answering this. Have you heard data that suggest to you that this drug is so potentially toxic to the fetus that it would prevent it being marketed. If you think you have not heard such data, your answer would be no.

DR. BENOWITZ: Are we doing both questions together?

DR. WOOD: No; just one question to start with.

DR. BENOWITZ: My answer I think that it could be marketed OTC with the proper warnings.

DR. WOOD: Maybe everybody should state it like that so there is no confusion.

Dr. Caprio?

DR. CAPRIO: Yes.

DR. WOOD: Why don't you state it like Neal did so there is no--if you are endorsing the Dr. Benowitz provision--

DR. CAPRIO: Yes; with Neal.

DR. WOOD: All right.

DR. BLASCHKE: A third for Neal.

DR. CARPENTER: A fourth.

DR. PARKER: Fifth.

DR. DAVIDOFF: I would not endorse on the basis of what I have heard so far.

DR. WOOD: So you are against Neal.

DR. DAVIDOFF: Maybe that, too.

DR. WOOD: I just want to make sure that you would not endorse this marketing under--

DR. DAVIDOFF: Right.

DR. WOOD: Okay. Good.

DR. PATTEN: I also would not endorse. Part of the problem, I think, is that, in this large number of women that have been exposed Rx, I have heard nothing about studies of the child post-birth developmental problems, behavioral

problems. We know nothing of that.

DR. McCLUNG: I agree with Neal, so I would endorse.

DR. CLYBURN: I endorse it as all.

DR. MAKRIS: I would endorse it recognizing that there are uncertainties and that the labeling may be able to handle that.

DR. SCHADE: I endorse it.

DR. TAYLOR: I would not endorse it.

DR. SCHAMBELAN: I would endorse it.

DR. WOOD: I am with Neal.

DR. TINETTI: I would endorse.

DR. WATTS: I would endorse.

DR. NEILL: I would endorse.

DR. WIERMAN: I would endorse.

MR. SCHULTZ: I would endorse.

DR. FINCHAM: I, too, would endorse.

DR. SNODGRASS: I would not.

DR. WOOD: Let's get a tally here. Oh; let me read to you the question--did you hear the questions? No?

DR. WOOLF: No; sorry.

DR. WOOD: We divided the issues into two questions. The first question was; have you heard data that suggest to you that this drug is so

potentially toxic to the fetus to prevent it every being marketed OTC under any circumstances. The purpose of that was to try and dissect out labeling issues, all of the uncertainty of that. So we are talking here about the biology, not the other issues.

The second question was; is the proposed labeling adequate to exclude women of childbearing potential from taking this drug based on the CUSTOM study or whatever else you have seen and, depending what you think about that, if you thought no, then we would want to know what you would want to see that would be adequate.

So we are not dealing with that question right now. We are just dealing with the first question.

DR. WOOLF: I think there is a potential problem.

DR. WOOD: Dr. Follman, did we get a--

DR. FOLLMAN: I would endorse it.

DR. WOOD: So we have 19 yes and 5 no. Dr. Clapp is not back yet.

Let's move on to the second part of that question, then, which is the more operational issue. The operational issue is, is the proposed

labeling adequate to exclude women of childbearing potential from taking this drug based on the CUSTOM study or whatever other data that we have seen out there.

Dr. Parker is not here but I am cognizant of the fact that there are other exclusions that we talked about coming back to later and we should come back to them later as well.

So, can we have some discussion on that? Go ahead, Dr. Makris.

DR. MAKRIS: I was just going to ask if, as part of this, we are going to be recommending some changes or just that some changes happen and that these be put forward by the sponsor.

DR. WOOD: I think we have the option to do both. I think the first question is to decide

if we think what was presented was adequate and, if not, then I guess I would imagine it would be helpful to the agency and to the sponsor to hear what kind of changes we would be looking for that would provide an adequate labeling package or whatever issues, a package that was used measure to the patient's understanding or whatever.

Frank?

DR. DAVIDOFF: I am not sure that I can think of package labeling per se that would reassure me enough because the CUSTOM study are really not reassuring. I would, however, be quite supportive of a behind-the-counter mechanism and I wonder if this discussion and this potential action might not be useful in that it might trigger a serious discussion and proposal for moving in that direction.

I realize the FDA or this committee doesn't have the jurisdiction on that, but, in terms of really getting a serious debate going, I learned, during the lunch hour, that, as I understand it, a number of states have actually now

legislated behind-the-counter mechanisms as legally empowered. So I wonder if that might not--the time might not be ripe to move in that direction.

DR. WOOD: Dr. Fincham?

DR. FINCHAM: If I might add, that is on a very case-by-case specific basis. It deals with, perhaps, cough syrups that contain codeine and other types of products so it is not across to board. It is certainly a case-by-case basis.

DR. WOOD: That is one issue to think about. There are others as well. Dr. Parker?

DR. PARKER: I would just say that, from a methodologic standpoint, I have concerns about both the label comprehension and the CUSTOM because I think, at the end of the day, what we are looking is to see can people understand what they need to know in order to be able to adequately self-select and use.

I don't think we have as much information about that as we need. One of the concerns that I have methodologically is that I think the real experts about product understanding come from

users, users and non-users. In the studies that were done, we really do not have insight from the population, for example, that self-selected to use incorrectly.

I think there is very valuable information that could be gained methodologically by approaching those studies differently. So I think that, really, what is required is more rigor methodologically to look at both label comprehension--I cannot understand doing a label-comprehension study and not making its results a part of an actual-use study saying that I understand that there were thousands that were tested prior to that.

But, unless the results of the label-comprehension study are perfect, then it seems like the results of that study could be fed into the actual-use study in order to make the label that then goes forward even better.

I think, certainly, the work that has been done in health literacy which points out that we have 90 million Americans--and I must say, given

the size of that number, many would say that that does represent the skills of "an ordinary American" whose struggle with very common, everyday tasks like using a bus schedule, that the task is daunting to take something as complicated as this and make it something that the ordinary citizen can understand.

The solution is not dumbing down the information because the information is too complex to be dumbed down. The solution is to figure out now to effectively communicate very complicated information that is absolutely essential for self-management. I absolutely do applaud the efforts to try to encourage self-management.

I think that the science, the methodology, has got to be so rigorous to advance our ability to communicate very difficult information and that is really where we are stuck. I think that the people who didn't self-select correctly and became users did so because they didn't understand what they needed to do. I can't imagine that they wanted to just go buy it and do it.

So I think it is going to take stepping back from that. The real experts are the users, the users and the selectors and non-selectors. We

are going to have to take that population and really partner with them to see what we can learn in order to get the kind of information that is really required for adequately being able to self-manage.

DR. WOOD: I have two--first of all, a Chairman's comment. I would like us to confine our comments at this point just to the labeling as it relates to child-bearing potential because we are going to come back to other labeling issues later. Then I have my own comments on this question, if I can make some.

I can't see how we can possibly say that the labeling is adequate given that only 1 percent of people got it right and not even the most liberal schools with great inflation and so on would allow to think that was a particularly great great. So I think the answer is that the label comprehension studies and others need to be redone.

But it seems to me that is something that could be negotiated between the FDA and the company. So I think they are not adequate right now. I can't imagine how we could say they were adequate given the data.

But I would like to, having said that,

suggest that we introduce very rigorous criteria for determining that women of child-bearing potential exclude themselves based on a label-comprehension study. That seems to me fairly easy to do, fairly easy to test, and it might have to be tested multiple times to find the right approach to do that.

Other questions? Suggestions? Charlie?

DR. GANLEY: I think the one thing that is worth having some discussion about in response to these answers, not just directed at the women of child-bearing potential, but when you think about, if you go to Dr. Shetty's review where it went down and it threw out the people where they made errors and you end up with about 10 percent, I guess what is somewhat difficult for that is that you have to

go through these multiple levels, one after another. I suspect that a lot of us wouldn't get them right in the end.

And so it becomes important, well, what are the important things that someone really needs to know in that hierarchy--what is your hierarchy here? Is it important that you know your triglyceride? Is it important that you know what your HDL level is. It is hard to understand why people didn't get the age thing right and there wasn't more information on that.

But I think, as you go through this and you keep asking questions and these different points are in different parts of the label, it is not totally surprising you get down to 10 or 20 percent. It is not surprising to me, in the actual-use study, that you don't have 100 percent.

But I think it would be important for us to understand what are the important things there that the committee thinks the consumer needs to know in that. Their cholesterol is important. Do they have to absolutely know their LDL cholesterol?

The British have a different model. They don't care what your initial cholesterol is. They do care afterwards, apparently.

But that is an important thing because half the people in her analysis, about 50 percent of the people, got thrown out because they did not get the LDL cholesterol right. Is that a dead-end then, if they can't get that? So those are the things, I think, that would help us in the course of answers.

DR. WOOD: I agree with that. I actually think that the entry criteria were far too rigorous and that a much larger proportion of the population would benefit from the drug and then were defined by that. I am not sure it is the least important for this population to know what their HDL was. I am not ever sure how important it is for them to know what their LDL was. I am certainly sure it is not important for them to know what their triglycerides are at that stage.

I think, to ask people to remember three numbers and kind of manipulate these is almost like

these tests for Alzheimer's that most of us would fail, probably, if we took it.

So what I am suggesting, I guess, is that we have a much more organized test that tests the things we think are critically important and avoid confusing people with a bunch of other information that they don't need.

Dr. Follman?

DR. FOLLMAN: I would like to talk about one methodologic issue in the CUSTOM study that I thought was sort of unfair and may have contributed to the low percentage of people being correctly classified.

So, if you look at the label, it says, do you know your numbers within the last year. So let's suppose a year ago, I got my LDL--

DR. WOOD: Hang on. We are talking about pregnancy right now just.

DR. FOLLMAN: Never mind.

DR. WOOD: So let's get to that because that is one of the questions down here. So let's just focus on the pregnancy issue. Any further

discussion on labeling for pregnancy? Yes?

DR. CARPENTER: Just looking at the current box, there is simply the statement, do not use if you are pregnant or breast-feeding. I think that message should be strengthened enormously. I think there should be a rationale provided. I think that people remember things better or pay more attention to them if there is some indication of the consequences.

I think some of the data presented this morning, although we don't have strict incidence data that we can use in a label, it certainly provides an association between not a simple or a limited defect but a very severe congenital defect. I think I care for some of the children with holopresencephaly and, believe me, it is not like anal-genital distance problems. With that association, some allusion to the severity of the consequences needs to be on this box.

The second piece is that the label is really the gestalt of the whole presentation and I think the sense that this is a natural product and

wholesome needs to be, perhaps, played down although it is considered one of the selling points.

DR. WOOD: Any other comments? Dr. Snodgrass?

DR. SNODGRASS: With regard to women of child-bearing age, it seems to me that you could think about the possibility of a large black-box warning equivalent. But then that still, perhaps, may not be 100 percent what you want. Then you could get into, well, can you, in an over-the-counter situation require pregnancy testing--I don't see how, logistically, that would be feasible in an OTC setting--but require pregnancy tests before you can purchase or use this product.

In the absence of that, then going back to saying, do a large prospective study of the 400,000 or whatever number of women are using this per year to look at outcome, actually, in depth, prospectively look at outcome because, if that data is pretty strong, then all these others become less

of a consideration, and it is strong that it is not a significant human teratogen, then these others become less of a consideration.

DR. WOOD: Dr. Parker?

DR. PARKER: Just as a comparison, I think the Heart Health Questionnaire that we used in the U.K. starts at the very beginning, I think, just as a model to compare in terms of clarity and ability to understand. At the very beginning, it starts with, are you male, 45 to 54, 55 and over, or female, 55 and over. If you are not, that is it.

It seems that the age alone relates very specifically to child-bearing potential. In terms of prioritizing the need to know in order to be able to do what you need to do, I would consider this as a model which was not tested in the currently proposed--

DR. WOOD: It also asks whether you have reached the menopause which would broaden the group a little bit and still prevent pregnancy.

DR. PARKER: Just an alternative model to look at.

DR. WOOD: It asks both, actually. Any other discussion? Dr. Makris?

DR. MAKRIS: It might be worthwhile just

beefing up some of the language about pregnancy because just asking the question or saying, do not use if you are pregnant or breast-feeding, that presumes that somebody knows already that they are pregnant. But there may be women who actually are trying to become pregnant and who are not pregnant yet and, perhaps, it should say, if you are trying to become pregnant or if you think you might be pregnant, to include those as well.

DR. WOOD: Or you think you might become pregnant, I guess. Dr. Woolf?

DR. WOOLF: I have a bit of a dilemma. One the one hand, we are telling people, women, not to take it unless they are 55 and older and unless you are in Italy and there are very unusual circumstances, none of those women are going to become pregnant.

On the other hand, how are we going to put on the label if, by any chance, you are less than

55, that you have to do something and you could get pregnant, what are you going to do about it? So how do you put that into a label?

If it is going to go into the label, I would strongly urge that it says that if you think you may be able to get pregnant, that you need to speak to your physician prior to starting Mevacor OTC. But I don't know how you deal with the two parts of that.

DR. WOOD: I think part of the problem right now, and the Chairman should shut me down, is that the exclusions and contraindications are mixed up with the indications. So, for instance, you are told not to take it if you have got heart disease. But that is not because heart disease is an exclusion. It is because heart disease actually means you must take it and you should be seeing your doctor to take it.

You are told not to take it if you might be pregnant. Well, you know, these are orders of magnitude different in terms of contraindications. One is a contraindication and one is not. So all

of that needs a lot of polishing and work it seems to me. But I agree with you. I think that could be separated out.

Any other comments? Do we need to vote on the question of whether we think the labeling is adequate? Does anyone think the labeling is currently adequate? If so, speak up.

We have had a discussion on the changes of the label that speak directly to the pregnancy issue, so I think we can pass--sorry; Dr. Makris?

DR. MAKRIS: I think it might be worthwhile to talk about the idea of recommending further testing although that was part of the question that was laid out here and a number of folks have actually brought that issue up. I think it is worthwhile maybe discussing it more.

DR. WOOD: Testing for--pregnancy testing?

DR. MAKRIS: No--well, additional testing, or additional studies, a prospective--

DR. WOOD: Oh; teratology testing.

DR. MAKRIS: Yes.

DR. WOOD: Oh; I see. Okay. Any

discussion on that?

DR. McCLUNG: I would propose that we wait and do that after we discuss the rest of the labeling issues. It is not specifically confined to the pregnancy issue and we have got more to discuss about that. At the end, I think that is an important thing for us to come back to.

DR. WOOD: Okay. That sounds like a good plan.

In that case, we will move on to Question 5. Question 5 is; does the frequency of appropriate self-diagnosis and self-selection support the conclusion that lovastatin 20 milligrams can be used safely and effectively in the OTC setting. Please describe which analysis influenced your decision.

Any discussion on this? Does that mean everybody thinks it worked? Dr. Woolf?

DR. WOOLF: This may be a radical approach but I think the CUSTOM study was a failed study. The way it was set up, only 10 percent of the population actually met the criteria. Half the

patients didn't have a cholesterol to begin with. For some reason, people couldn't understand their age and then we can debate whether it is important to know your HDL or not.

So, if you simply look at the study from that standpoint, the answer was that it didn't work. If you then add a whole bunch of ad hoc analyses after that and add some common sense, you say, well, people selected themselves properly. But that is equivalent to saying, well, why did we do the CUSTOM study at all because we can just use some common sense. If you are middle-aged and you are overweight and you have a family history, you probably have an elevated cholesterol, and your cholesterol is too high and you ought to do something about it.

So I don't the CUSTOM study was terribly convincing at all. So, therefore, I can't use it to support the over-the-counter indication.

DR. WOOD: Okay. Any other discussion? Mary?

DR. TINETTI: I have some concerns as

well. I think the problem is that we are talking about this new model of long-term treatment for an asymptomatic condition and, unfortunately, the actual-use studies are still in sort of the old paradigm. So, almost by definition, they are not set up to answer the kind of questions we are interested in.

But, in addition to that, is, even in the best scenario, people who volunteered to be part of this study and had incentives to participate had a difficult time self-selecting and most of them said they had to talk with their physicians which, again, begs the question, is that an over-the-counter medication.

In addition to that, there is a small number of older people--the low literacy was set at eighth grade which is probably higher than what most people would consider low literature. So I think, in many levels, this study does not address the questions that I think will be important in determining over-the-counter.

DR. WOOD: Any other discussion? Dr.

Follman?

DR. FOLLMAN: This is a point I tried to make earlier. It has to do with defining who met criteria or not. According to the label, if you have your cholesterol test done within the last year and your numbers are acceptable, and you meet the other risk criteria, you should take the product.

That is not the way things were counted here. Let's suppose that three months ago, I took my LDL and it turned out to be 150. Let's suppose I meet all the other criteria for the test.

I go to the CUSTOM study, get a finger-stick test and it is 182. Now I am not any longer eligible. I would be counted as a did not meet the criteria. I think that doesn't make sense to me because, according to the label, I should be meeting the criteria. Within the last year, my numbers were in the right.

We know that the cholesterol numbers will bounce around both because of reproducibility errors and because of changes in time over the

course of the year. So I think, in some sense, the methodology was overly harsh in defining who was eligible or not.

DR. WOOD: Dr. Clapp?

DR. CLAPP: Does the REALM literacy test test for comprehension? You can read, but do you comprehend. So I was wondering if there is a comprehension component to analyze for--

DR. PARKER: No. The REALM is a list of 66 words. It is a word-recognition, pronunciation, test. You read the list of words. If you correctly pronounce the word, it is scored as correct. It has not measurement at all of either comprehension in context and there is no gauge whatsoever of numerancy which is the ability to understand numerical concepts which are a critical piece of the understanding needed for acting on this kind of information. So a stronger screening would, no doubt, give you more information about the population.

DR. WOOD: So does that mean I would fail on the pronunciation?

DR. PARKER: I don't know but I will test you afterwards.

DR. WOOD: On the pronunciation.

DR. PARKER: But I am going to use my instrument and not that one.

DR. WOOD: Any other--Frank?

DR. DAVIDOFF: I guess I am a little bit confused because it seems to me that we are getting too different messages here. One of them is the entirely laudable effort on the part of Merck to have the target conform to the ATP guidelines to minimize confusion, to presumably increase the efficiency and efficacy because it is more targeted.

At the same time, we are hearing that, well, there was an awful lot of slipping in people self-selecting for that target group. But that is okay. In fact, it is good because then those people will also get some benefit.

So, in a way, the latter observation suggests, well, why have these criteria or why have many of them because, as Chuck Ganley says, well,

if some of them aren't very important, why put them in there.

Well, I think the reason they are in there is because of Merck's interest in keeping things more targeted and more consistent. So I am a bit hung up here between those two. I would appreciate anyone's comments, particularly, perhaps, from the sponsor as to what is really going on here and, perhaps, reassuring us that this is going to be going in one direction or the other rather than sort of like the character in the novel who jumped on his horse and rode off in all directions.

DR. WOOD: Do you want to respond to that?

DR. HEMWALL: Yes. I think it would be helpful if we had a few minutes to try to return back to the center in the sense that people are thinking very closely to what the FDA analysis did, which did take that very strict interpretation. If you missed any of the ten or twelve criteria, you went down into the bucket of "failed."

Of course, one of the elements was the doctor interaction. That doctor interaction was

also a key element of the label-comprehension study and that 1 percent rapidly goes up when people say they would need to check with their doctor because, of course, in a label-comprehension study, we had a bunch of people that didn't know their cholesterol numbers. This was a mall-intercept study.

But Bob Tipping would like to just take a few minutes to come back and actually show that this is, in fact, how the data were analyzed. Although we took a very strict approach to stay in line with the NCP guidelines, we looked at that data in other ways that allowed some leeway around those guidelines knowing that it is still a surrogate and we are trying to approximate a surrogate with our labeling.

MR. TIPPING: I have several comments to make. I have heard several comments here about our behavioral data and our comprehension data. Some of them I agree with and some I think need some clarification.

Dr. Ganley has made a few really good points, I think, in his opening remarks the other

day. He made the point that the health consequences of the errors must be considered. Then, later today, he made the point that there are errors occurring but there has to be some hierarchy.

I think that is exactly what some of the analyses that we presented tried to do, tried to put some context around that. It was a full disclosure. We told you about the safety warnings but then we tried--and, actually, I believe that the label performed extraordinarily well both in the consumer's ability to comprehend it as well as behave to it.

I will show you some slides in just a minute on that. The areas where maybe the behavior was a little bit less was around these very criteria that we are targeting the population, do you know all your lipids. What are your triglycerides? That is where the behavior was a little bit lower.

I don't think--to respectfully disagree with what someone on the panel said, I don't think

that is because it is a strong lack of comprehension. I think people from our label-comprehension studies understand those messages.

I think it boils down to them making their own personal assessment of benefit. They don't have the safety issues. They know that maybe while they don't know all of the issues on this label that have to do with the targeting a population, I don't know what my HDL is but I know my doctor told me I had a high total cholesterol. In fact, 80 percent of our users knew their total cholesterol.

They decided that, I am going to give this product a try. I think that our analyses tried to break that out and it showed you that greater than 90 percent were getting this safety-warning messages, and that number fell to the 60s for the label-benefit criteria.

I think the FDA analysis, which we don't argue with the numbers that underlie all of it, but it was very much a hierarchical approach that

required compliance to each and every one of those elements.

To Dr. Ganley's point, I am not sure that that approach takes into account the clinical consequences of behavior around those elements. So, with that sort of passionate speech to start things out.

DR. WOOD: Dr. Benowitz? Oh; I'm sorry. Dr. Neill first.

MR. TIPPING: I would like to show you a few slides.

DR. WOOD: I'm sorry. I thought you were finished.

MR. TIPPING: I will hurry this along.

DR. WOOD: Be quick.

MR. TIPPING: If we could see Slide 122.

DR. WOOD: Very few slides. Okay?

MR. TIPPING: Okay.

[Slide.]

Again, this is to remind the group of a slide that I showed in my presentation which talks about behavior around the safety warnings in the

label. They are listed as warnings for the initial use. You see many of the evaluators with these conditions and very few, the yellow bars, that are actually using it. 80 people who came and said, I have liver disease, only three used.

That, to me, is a lot better than 10 percent behavior around these elements. Twelve pregnant women; none of them chose to use. This had nothing to do with a physician interaction that mitigated this behavior. Those twelve pregnant women chose not to use the product.

Potentially interaction medications. There were 152 of our evaluators. Only ten of them chose to use and there were no--and this gets me to another point. So that is behavior around this element, but you have to put it in context. What is the absolute risk to this group of people?

We have heard that people taking potentially interacting medications with Mevacor, maybe the rate of rhabdomyolysis is 1 in 50,000 patient treatment years. So you have to kind of look at that and say, with that background rate, if

there is this population of people that are at risk doing that and we keep this many from doing that, then you have to apply that factor. So the rate would drop from 1 in 50,000 or 1 in 100,000 patient years if we take 152 of the 162 that would expose themselves to that risk out of the equation.

So I think, in interpreting some of the behavior, I think we have to be careful to put it in context to the actual extremely low background rate of the actual adverse experiences that we are worried about here.

Let me do one more slide. Give me Slide 1604.

[Slide.]

This slide specifically talks about the people that came to one of the sites with a history of muscle pain. The label is very clear and its message is about that, don't use the drug, talk to a doctor.

One point I would like to make is that the label is effective in raising awareness of this issue because 300 of our evaluators, nearly 10

percent, came and said, "I have had a history of that." So it is very important. I think the level is effective in raising that level of awareness. And it is working, to a large degree, and that 5 out of 6 of this 300 didn't use the product. 53 did.

What is the consequence of that? Well, 13 of the 53 reported some drug-related muscle symptom during the study and, again, how much did all of the label messages kind of raise the awareness of that.

But, then, what is the behavior in this group of 13? It is a small number of people but 11 of the 13 make the appropriate decision to stop and stop taking the product.

So I just wanted to show a few of these slides to say that there is another interpretation of our behavior looking at specific elements of the label that are of particular concern and I think we actually have exceptional behavior.

DR. WOOD: Okay. Dr. Neill.

DR. NEILL: If you are over 45, and you

are exercising, as everybody is that takes this medication, and you don't have muscle pain, I want to know who you are because you are not doing the right exercise.

But, more importantly, I think, among those users who reported these symptoms and chose to take the medication anyway, we haven't seen data regarding the attitudes that inform their decision to use this despite whether they comprehend or don't comprehend.

I feel confident that there may be some who choose, as a result of this proxy, the box, which is a proxy for informed consent which, of course, in a physician's office is detailed, rigorous and perfect. But I am confident that people who see this box and use the information on the box in the process of using it as a proxy for that informed consent that some of them recognize those symptoms. They know they have diabetes. They know they have these other high-risk conditions and choose this because they can't get any of the other things because they are not

insured.

They can't get any of the other things because they just don't have insurance this month. I do think that, in part, some of those attitudes inform what may of us have as an opinion regarding the potential public-health benefit. I don't think that we should let it be lost that, however small that effect may be or however few those patients may be, who really should be treated at a higher dose and really have to see their doctor.

The bottom line is, they don't. If they get some benefit from this, that is better than nothing. The question seems to be whether it is worth the risk to somebody else. Is the risk of them receiving some small benefit and not dying this year from their massive heart attack, even though they have metabolic syndrome and all the other things for which they have not seen a physician, and if you have any concern that there are patients with metabolic syndrome that don't see physicians, come to my neighborhood.

Walk down the street. I will show you 20

in five minutes. They don't see physicians for this and are not being treated. I do believe that there is some benefit for that. So, for me, while a strict reading of this Question 5 and especially the detailed analysis that Dr. Shetty presented yesterday suggests that people do not appropriately self-select according to every criteria on the label.

I still believe that patients within the CUSTOM study have been able to glean the information that they need to tilt that risk:benefit equation towards benefit. I admit to there being some degree of faith in that given that the benefit to me is not one I can measure for an individual patient but it is a benefit that accrues from the use of this medication in the OTC setting at the public-health level.

When somebody wants to fund that study, let me know. I would be happy to be a P.I. for you.

DR. WOOD: Dr. Wierman?

DR. WIERMAN: The majority of the focus

and the discussion recently has been in the CUSTOM study about how well it did to prevent people who would be at risk for the side-effect profile from getting the side-effect profile and the absolute low risk of potential toxicity of the drug.

I was more concerned with the FDA presentation about how poorly it did in having people correctly self-select for the target population. So how well--the data suggested that the people who this drug is appropriately targeted for in the appropriate label did not pick it. So we have talked about how well it did in preventing people from getting side effects.

But I would like to refocus the question on was this an adequate evaluation to prove that we have developed tools to be able to allow the population to self-select the drug for the appropriate reason, to take it for the right reason instead of potential risk.

DR. WOOD: Dr. Benowitz?

DR. BENOWITZ: I think a lot of the issues that I was going to talk about have been dealt

with. But I guess the question, as asked, doesn't exactly say, according to the labeled criteria--because I think the CUSTOM study, as everyone says, has got a lot of problems, especially self-selection based on lipids.

But there is evidence that it is pretty safe, especially if they can deal with the age issue. And the efficacy, if you do look at a shift of LDL cholesterol, there is the same shift of cholesterol in the population as has been seen in controlled clinical trials with a 25 percent reduction of LDL cholesterol.

So one could say that that is effective. I guess I need some guidance as to how to answer this question.

DR. WOOD: I agree. The problem with the question is, I think, the committee doesn't buy into the criteria that were used for entry into the study in totality. Is that fair? We don't buy that and we actually think it should be more liberal, just so everybody understands that. Therefore, we are not enthused by the problems that

occurred in the study because we think that knowing your triglycerides, while it may be a good thing to know, it is sort of analogous to somebody knowing their American Express card off by heart. It may not help much to get your lunch.

So that, I think, is kind of getting at--Charlie, you already address that, I think, to some extent. Do you want to add something?

DR. GANLEY: I think you are getting at a different issue because I think you are going down the path a little bit that why even have a label that has instructions if we can sort of come to the compromise that anyone who takes this is going to get a benefit as long as we kick out the people who may be at increased risk.

I think it goes back to some of your opening remarks, you know, the population versus the individual and who needs to be eliminated. Obviously, the less information you have on the label which has criteria directing it towards a certain population, you are going to expand the population, potentially, if he takes it and is that

okay.

But I think, in the context of what our interest is this study may get based on the criteria that is in that label right now. That is what I was trying to get at. If you have it--my earlier remarks are it is tough. You have all these layers to go through--Dr. Parker could probably talk to it better than I can--and that is just hard to do.

So, if you say that it doesn't make it but--I don't really think you need to know your HDL level, or I don't need to know your triglyceride. That starts peeling away the layers. Dr. Parker may be able to articulate it better than I can. But I think, in the context of what our interest is, we have a label. These were the population. You may not agree, necessarily, with that population, but does this study show that they self-selected well with that.

That is the question. Then you can add all your caveats, what you think is important, what is not important, which gets down towards your

path.

DR. PARKER: Just to sort of take up on that, I think published studies would support that when messages are layered, the first layer is the one that is going to be most likely to be understood and, with each additional layer, which is another way of defining complexity, you lose comprehension on the other side.

The challenge here, as I said earlier, is that the required information is complex. I think the burden, then, is to say, well, what is the absolute essential information to know. I would put beside that--because the need to know is the term that we use so much, but for the activated consumer, it is not just need to know. It is need to do. What do I need to do?

So you have got to sort of put those side-by-side when you approach the content of information that needs to be defined. Once you are absolutely clear on the information that is essential from a need-to-know, need-to-do standpoint, then it is a matter of figuring out how

best to communicate that complicated information and yet it would be great to dumb it down.

But that doesn't work. It is too complicated to dumb down. There is a set of information that people need to be able to understand and act on and there is a way to communicate it. But it takes rigorous work, rigorous scientific data, to prove that you have actually done that.

What I would contend is that there is a beginning to that process but that process is going to require the same type of rigor that has been applied to the other outcome studies that look at biochemical markers like liver-function test and like neural-tube defects or whatever it is. It takes scientific rigor to really figure out what it is that has got to happen so that we can take advantage of what we know biochemically or biomedically.

We have got to have that degree of rigor in our efforts to communicate it effectively.

DR. GANLEY: I think Dr. Wierman put her

finger on the key question, and that is the consequences of selection for rather than selection against because I think it is pretty clear from the CUSTOM study that the ability to select for being in the target group was quite variable and fairly weak, and so on.

I don't' see that as dangerous in the sense that it is putting people at risk, necessarily. But I think it does raise the key question of whether not meeting those criteria doesn't dilute the efficacy of taking the drug. In fact, I think that is exactly right. I think that, in a sense, is the key or a very central question.

Every time you don't meet one or another of those criteria, the amount of benefit you can expect from this gets less and less. That, I think, multiplied times millions of people is an enormously important question.

DR. WOOD: Any other discussion on this? Is this a question you need a vote on or have you got what you need out of this? All right. Then, if we are ready, any other discussion? Let's have

a discussion about the question. Sorry; go ahead.

DR. SCHAMBELAN: I think the question is still unclear.

DR. WOOD: Yes; I do, too.

DR. SCHAMBELAN: I think it would be interesting to come back here in six or seven or eight years and talk about the poly-pill and not having any criteria for taking the medication. So I think people are comfortable because we recognize that lowering LDL cholesterol probably at any level across the spectrum of these patients is going to be beneficial.

But that is not what you are asking us. You want us to know if this self-diagnosis technique that was used here was adequate to support a conclusion. I think I agree with Dr. Woolf, that I think this was not a very good study in terms of providing that support.

But, as to whether we think it could be used safely or effectively, I think we have already addressed that in the earlier discussion. So it would help if you could either break that question

down or make it something that we can vote on without having that ambiguity.

DR. WOOD: I agree. I think that is spot on. It seems to me that the committee has a comfort level for the use of this drug that goes beyond the criteria that were used to define that use study; is that--so that makes it somewhat difficult to take what looks, then, like a much more difficult and exact requirement than they think is reasonable. Is that--

DR. SCHAMBELAN: Yes.

DR. WOOD: Okay. So I am not sure how we vote exactly on that. Sorry; somebody over wants to say--

DR. McCLUNG: I would like to then beg out of being included in that last statement of yours about the committee.

DR. WOOD: Okay.

DR. McCLUNG: I am not comfortable with the documented efficacy in much lower-risk populations. Again, sort of in mention, that the ability in the CUSTOM study of patients to identify

themselves on the appropriate inclusion criteria, and inclusion criteria were chosen to identify patients at moderate risk.

26 percent of the individuals made the right selection on the basis of age and their LDL level, the two major risk factors that we--and the way in which they missed the target was that the patients were younger and the majority of the LDL misses were that their values were lower, both of which lower the risk in the population which means that, despite--I am not arguing that relative risks won't be equivalent in that population, but the absolute risk and, thus, the benefit and the efficacy of therapy is diluted by the decisions that were made.

The risk remains the same, the risk of side effects remains the same, in that population but the benefit with regard to reducing heart disease is diluted. As that happens in what I think is probably the best-case scenario in the CUSTOM study, and once we have direct-to-consumer marketing in a much broader population, I am not

confident that the behavior is going to be better in that circumstance, in that scenario, than what we have observed in the CUSTOM study.

Then we are treating a very low-risk population where the benefit is modest, to be generous, and the risk remains the same as was seen before. So I am not certain I agree with you

DR. WOOD: I think I was saying knowing your HDL, knowing your triglycerides, probably doesn't influence that risk very much.

DR. McCLUNG: That's fine. But even if you take the two important easy, what I would contend to be the crucial pieces of information, age and LDL, 74 percent of patients miscategorize themselves as being candidates for therapy.

DR. WOOD: It is hard to imagine, and Charlie Ganley has made this point already, how such a large proportion of patients get their age wrong and give it right presumably in the entry form to the screener, because it wasn't that someone knew their age.

DR. McCLUNG: It doesn't say they got

their age wrong. They knew their age but they made the wrong decision, by the criteria that were set up.

DR. WOOD: Why don't we go you, first.

DR. SCHADE: I would just like to say one thing. I like the CUSTOM study. I think it was a good study. I think what we are forgetting is there is there is no control group. I think the de facto control group that we are all thinking about is 100 percent correct answer to each question.

The fact is, a control group might be a fully informed person with medical background, great experience with lovastatin, et cetera, et cetera, and, if you have that control group, I am certain you still wouldn't have 100 percent correct answers, not if you have to add all the criteria that are listed.

So I actually think the CUSTOM study--nobody knows, or at least nobody can tell me, is what the correct study should have been relative to the correct answer. In other words, let's suppose only 10 percent of the people got the

entrance criteria correct. Well, what number should it have been in the best population that we could have picked for a control study.

There is no control study. A control study, of course, is really practically impossible. So I think this is a descriptive study that gives us information. We may not like the answer. I don't think anybody liked the answer that everybody didn't get every question right. But I am not so sure that this is a bad study. I think it is informational. I think it may lead to positive suggestions on correcting the literature that is given out and I think that is a positive outcome of the study.

But I don't think we ought to--at least, personally, I think it is a very interesting study with a certain outcome. I don't know what should have been the outcome but I think, basically, it is going to lead to some positive suggestions. So, rather than criticizing the company for doing the study, I think they should be basically applauded but say, gee, we would like, maybe, some more

information we didn't get from this.

But I don't see a control group for this study so I don't know what the right answer should be.

DR. HEMWALL: Thank you. I think I have a couple of things that can put all of this kind of in the right perspective and bring together everybody's remarks here and kind of put people in the mind set that we were in four years ago when we set about to define the label population and we worked with FDA on that. We worked with outside cardiovascular primary prevention experts.

How do you develop a label that attracts the population that is consistent with ATP 3. What we did was we thought kind of conceptually. You want to drive them down the middle of the highway and keep them from veering off onto the shoulder. So you want to make the guideposts very strict, make sure that they are catching their HDL, we are doing it in terms of LDL instead of total cholesterol which most consumers know and we are asking them to know a lot of other things about

themselves.

But we are guiding them down a narrow path. Unfortunately, some people chose to go a little bit outside that path but that is a good thing because we want to stay within the spirit and intent of the guidelines.

What we are dismayed a little bit by is that we are sort of being criticized or punished by those that did go a little bit outside the guidelines. But the interesting thing is, if you look at all the people in CUSTOM taken together, 70 percent of them met ATP criteria that would qualify them for lipid-lowering therapy.

Their overall 10-year risk was around 10 percent. In AFCAPS, the 10-year risk, and it is a slight extrapolation because that was a 5-year study, but the 10-year risk of the placebo group for heart CHD was about 6 percent. So we are still in a range where AFCAPS has demonstrated a benefit which can be linked to this group, albeit not directly, but we are in a group that can benefit.

If you take away the restrictions that the

label applies and just look at who was interested and used the drug, 75 percent of them were in accordance with ATP 3 criteria. We think that is pretty good. And, by the way, two-thirds of them got their lipids tested and came back and followed through with some of these more difficult elements to just actually execute let alone know about yourself or your risk factors.

So we were very pleased with the results of the study but, taken very strictly, keeping people down the narrow highway, we did not have everybody on the highway. Some were driving on the shoulder, but we kept them out of the ditch and that is the most important thing.

DR. GANLEY: Alastair, can I just add--I think the thing is, and maybe just to put it in another framework, you have this CUSTOM study and you have these multiple analyses one of which--it seems--I don't know, but it seems that you are comfortable with these other analyses where it defined people as closely benefitted or they fit the ATP.

So when you look at a net--if you go back to Dr. Shetty's slide, you get up to 900-and-some of the 1059. So, if that is what makes you feel

better, then you buy into that analysis. That is what I think we are trying to get out, because it says, please describe what analysis influenced you.

That is what is influencing you. You think that that is a reasonable way to look at that, potentially. There is the other side where, well, we want some a little bit stricter. We want people to follow that. That gets closer to Dr. Shetty's or if you want to even add on the physician override. Do you understand what I am saying?

DR. WOOD: Absolutely, but I think we are also hearing from some of the committee who feel, as I understand it, uncomfortable with that. So we need to have that discussion so that we get that clear.

Maybe we should articulate the question, rather than in terms of results from the CUSTOM study undefined, and redo this question the way you

just described it so that, as I understand the question that you are putting out there, is would you be comfortable with the results of the CUSTOM study in terms of the people who took the drug and their likelihood for benefit. Is that the--

DR. GANLEY: To me, it gets still back to these multiple analyses. If you take it on face value, you have this very strict interpretation which gets you a 10 percent. When you start throwing in these other things where, yeah, well, they missed a few of these things but they had this, so that is okay, and you keep adding to that pile.

I think that is really consistent with what people are saying here. They think that the population may not be right but they had a comfort level with how the study was. And that, I think, gets back to the Merck analysis of, well, when we look at those people and what their risks were, they still fit the NCEP/ATP guidelines.

So someone could say, for this study, yes, because I buy into that very loose interpretation

of the analysis or, no, because I am a little more strict. That is the question, I think, to be answered. If you say yes or no, what analysis made you say that. If you are comfortable with this alternative analysis where it is closely adhered to the label for benefit or the ATP guidelines, you are getting back into this realm, well, I don't think the population's right but that is okay.

DR. WOOD: So you want us to address that question because I don't want to--

DR. GANLEY: Yes; I think it is an important question for us to understand because it gets to people's hierarchy, too.

DR. WOOD: So the question then, really, is, are there strict constructionists who feel that the only analysis is the total analysis, or are there people who feel more comfortable with an analysis that looks only at the key risk factors and how do we break as a committee on that. Is that what you are--

DR. GANLEY: I don't like to rewrite questions during the meeting but I think if we just

stick to the question and think, do I fit into this looser interpretation analysis. Then I am getting up to 90 percent correct self-selection. Or am I very strict "look at the label," and I am getting down to that 10 percent.

That will help you decide what your answer is. If you are up at 90 percent, that may be--

DR. WOOD: But I am trying to operationalize this question. So the question would be that people could answer yes to Part 1 or no to Part 1 and base that on either a strict constructionist sort of analysis, so there response could be, I base on a strict constructionist analysis. Every criteria has to be counted, or a looser criteria. Would that be fair?

DR. GANLEY: Yes.

DR. WOOD: I mean, that seems like--I mean, we have to get answers. Do people understand our discussion? Let's start with Dr. Snodgrass.

First, is there any further discussion we should have on that?

DR. WATTS: I think it is a misnomer to

call this self-selection because many of these people talked to a health professional and, yes, they made their own decision, but it is not that they read the thing and they came to the right conclusion. They needed to get help and help is not mandated in this scenario.

So I am uncomfortable with the fact that many of these people needed to access other resources before they could "self-select."

DR. WOOD: Okay. We will strike "self" in both places so the appropriate diagnosis and selection support--how about that? Would that be okay?

Any other discussion? Then let's start with Dr. Snodgrass.

DR. SNODGRASS: Question 5, I will answer no.

DR. FINCHAM: No.

DR. WOOD: Wait. There are two questions we are being asked. Sorry. Back up again. We want to know--sorry. I think what they want to know--

DR. SNODGRASS: What were my reasons.

DR. WOOD: --if, if you answer yes or no, are you basing it on a strict every-criteria

analysis or a looser analysis that only took the major risk factors. I think that is what Charley--is that right? Okay. Let's go again.

DR. SNODGRASS: So probably I fit the stricter group, perhaps. Their specific section is 55 percent, I think, had greater than one risk condition, used the product but still had relative contraindications, as an example. To me, the package information--it has already been discussed. This is very complex and it is just a complicated issue. So that fit into this.

I think it turned out something like 69 percent needed more information to really make a decision based on what was presented to them.

DR. WOOD: Okay. Jack?

DR. FINCHAM: My answer is no, based upon I don't feel that the CUSTOM study is generalizable past the participants in that study. I am not trying to criticize Merck. I am not trying to

criticize the people that conducted the study. They are not bad people. It is just that this was a flawed study from the git-go. That is why I say no.

DR. WOOD: Dr. Schultz?

MR. SCHULTZ: My answer is no. As an individual, I feel, as Dr. Neill said, how many of these people actually went to their own physician or a physician to get to the point where they could make this informed or self-determination?

DR. WOOD: Dr. Wierman?

DR. WIERMAN: I answer the question no, with more strict criteria.

DR. NEILL: I answer the question yes and the only reservation that I have in that answer is the recognition that, in answering yes, I don't believe that people have to understand why they are doing the right thing to do the right thing, A. B, I do buy into the analysis that suggests that there is medically acceptable use that falls outside of the label criteria. The only reservation that I have about that is a very practical one. As a

prescriber, if this goes over-the-counter, I don't have great hope that prescription benefit managers will alter their OTC versus prescription criteria in a way that will allow me to continue to use prescription statins in the way that I need to and, if there is a reason that I want these strict criteria on the label and on the approval language, it is so that I don't have to add to the stack of prior authorizations that I and my patients hate, and we will have them if these criteria are loosened because every patient that is on a statin needs to be on a statin, needs to be on a higher dose, needs to be on a prescription and will be made to jump through that hoop first and nobody in here wants to do that.

Having said that, I am still answering yes.

DR. WATTS: I would say no. It is hard to point to the analysis. It would be helpful if we had a list of the analyses we are supposed to be considering labeled A, B, C, and D. I an not a strict constructionist but somewhere short of the

liberal. I am concerned that many people self-selected or made the determination to take the drug who didn't have substantial opportunity to benefit from the drug.

DR. TINETTI: I say no based on two things. Number one is most people did not do this by self-selection. They needed help and input. The other reason I say no is something that sort of got swept under the rug is how many people who are presently on prescription medications will no longer want to take their prescription level, will go to this lower level, based on what Merck has told us, that these people prefer to self-medicate.

My concern is that CUSTOM didn't address all the questions that are necessary.

DR. WOOD: I vote yes, on the more liberal criteria.

DR. SCHAMBELAN: I vote no, on the stricter criteria.

DR. TAYLOR: I vote no, on the stricter criteria particularly for the low literacy and the minority group. I think there are problems

lurking.

DR. SCHADE: I vote yes, on the more liberal criteria.

DR. CLAPP: No. 37 percent of women users were less than 55 years of age and 69 percent needed more information. That fact is disturbing to me because I am not sure whether or not they actually received this or tended to receive it because it was a more comfortable box to check.

DR. MAKRIS: No, based on the more conservative criteria.

DR. CLYBURN: No, based on the fact that I think that the low-risk population is not apt to get a lot of benefit and they would still be subjected to risk.

DR. McCLUNG: No, based on either the stricter or the liberal criteria.

DR. PATTEN: No, based on the low percentage that selected correctly based according to the two most important criteria, and also no because of the fact that 37 percent of the women who were selected were under 55 and 11 percent of

women under the age of 45 selected.

DR. DAVIDOFF: No. I think the strict constructionist versus loose analysis is looking at the problem through the wrong end of the telescope. I think the important point is the potential efficacy and it seems to me that that was demonstrated by the CUSTOM study to be quite weak whether you interpret the choices were made by the strict or the loose criteria.

DR. FOLLMAN: I would say no. Some of the things that I found more troubling were the fact that it seemed about two-thirds of the people were outside of the intended range meaning they would be either overdosed or underdosed, that about 10 or 11 percent of the women were less than 44 and that only one-third of the people got the six-week test, so they didn't seem to be able to follow the directions in terms of monitoring their cholesterol levels.

DR. PARKER: No, but I would add that I think data gleaned from the label comprehension and the CUSTOM study are a beginning.

DR. CARPENTER: No, based somewhere in between the conservative and liberal criteria but primarily being very uncomfortable with the ability

of a generalized population to make appropriate decisions without the help of physicians in many of the cases.

DR. BLASCHKE: Yes, with the caveat that I, too, am concerned about the percentage of women of childbearing potential that did take the drug.

DR. BENOWITZ: I would say yes. I share the points of view about why the age was not followed. It seems like something that should be correctable. I do agree that there are some people who probably took treatment with low benefit because they were at low risk. But, on balance, I think that, for the most part, it was safely and effectively used.

DR. WOOLF: No, because there were too many people who would have the most moderate benefit participated and their failure to follow up with lipids sufficiently, lipid measurements.

DR. WOOD: So 6 yes and 18 no.

The next question addresses the supportive role of a physician in what has been described as self-selection or self-diagnosis although Dr. Neill, I think it was, made the point earlier, or somebody made the point--Dr. Watts, I guess--that it is not really self-selection if it is with a

physician.

I will read the questions to you. A high percentage of study subjects in the CUSTOM actual-use study relied upon a physician for correct self-selection and/or self diagnosis--at least said they relied on a physician. I think that actually should have been in there because we don't really know that. Do you expect the general population will have this degree of physician interaction? Do the CUSTOM actual-use-study results support a conclusion that individuals can use lovastatin safely and effectively in the OTC setting without the guidance of a physician?

Do we have discussion on that?

Apparently we have to correct the vote. It was 5 yes and 19 no.

DR. BENOWITZ: It was my understanding that, for Part B, that the guidance of a physician was intended for certain people.

DR. WOOD: Right. I didn't understand that question either. My understanding of the package is that they are going to suggest that people get a physician involvement if they want it and, if they get that, that is not a failure.

DR. GANLEY: I think that was more

directed at the population of people who do not have a physician. It gets back to, you know, this--I am not disputing that it is good to talk to a physician but there is a significant proportion of the population that does not have that choice. I think that is where we are trying to get at because Merck's analysis of correct self-selection was the people who followed the label and then this physician override.

Well, if you don't have a physician to override, what do you do?

DR. WOOD: What was the proportion of people in the Merck study who didn't have a

physician?

DR. GANLEY: I think the important thing, though, is to understand what is the percentage of the population that doesn't have a physician and have access to a physician.

DR. WOOD: No; I understand. But let's hear what they have.

MR. TIPPING: Of the users in CUSTOM, 57 percent of them at some point in the study had an interaction with a physician. Now, it is important to distinguish that from an interaction that actually had some influence on our judgement of self-selection behavior. So it is 57 percent with an interaction, but there were actually 620 of our 1,059 users whose behavior around that initial decision did not require a physician override.

I guess I would add to that that those are what we feel are the important criteria, the warnings. That is where the behavior and the entire cohort was 90 percent or higher. But, we don't think it is the right thing to do because we feel the physician is mentioned in the label and

that is appropriate behavior.

But, if you do look at just that subset that didn't require that physician override, that 620, it is 82 percent.

DR. WOOD: Let's keep moving here. The question that you were asked, though, was what proportion of patients in the study had a physician. Do we know the answer to that or not?

MR. TIPPING: 57 percent--

DR. WOOD: No; they are the people who saw a physician. They might have had a physician and been able to go see a physician if they--I know that. So 80 percent, Dr. Wierman is pointing out, had insurance; is that correct?

MR. HANSON: I just want to make sure I understand the question. It was how many of these--

DR. WOOD: The question that we are being asked to answer is do you expect the general population with this degree of physician interaction. In determining the answer the answer to that, I guess, the question devolves to, was the

population you studied fairly representative of the U.S. population in terms of the people who had insurance and, therefore, had access to a physician.

So that is what we are trying to get at, I think.

MR. HANSON: I will just give you the data. Of the people who were in CUSTOM, 90 percent had seen a doctor within the past year and that is certainly higher than the general population which is consistent with--what we have said is these people are very involved in their healthcare and with their doctor.

As far as health insurance, I would have to look that up but I can get back on that.

DR. WOOD: My recollection was you said 80 percent.

MR. HANSON: Yes; 82 percent healthcare, 50 percent had prescription coverage as part of that.

DR. WOOD: Say it again; I'm sorry.

MR. HANSON: I'm sorry. 82 percent had

health insurance. 50 percent of those had prescription coverage. I don't know how that compares to national averages.

DR. WOOD: Okay. It is about the same, 40 million people are supposed to not have health insurance.

Neal?

DR. BENOWITZ: Just another question about b. It says, "without the guidance of a physician." But, to me, if there is a pharmacist available or if there is a knowledgeable 1-800 number, that would really affect my decision about this I think a pharmacist could do the same thing, or a knowledgeable 1-800. So, could we expand this to some "health provider?"

DR. WOOD: So we will read that as 1-800-doc and a pharmacist.

Dr. Parker?

DR. PARKER: It was very much on that same point, just that there are so many mentions of the study personnel and I understand from yesterday that that is because this was the label used in

CUSTOM and it is not the label that would be used in actual use, necessarily. But I think that is a point for clarification and also for understanding.

I think there would be many ordinary Americans who would not know what study personnel means. I can tell you they don't know what a healthcare provider is. We have done that and taken a close look at that. Physician is more understood but the notion of who that intermediary is, if this is the role of an informed intermediary, being very clear about that.

I still have some concerns about--I guess the answer yesterday was this notion of the study personnel would be taken off the label were this the label to go to market, that it was only tested for CUSTOM. But I still have some concern about that.

DR. WOOD: Are we ready to--sorry; Dr. Clapp?

DR. CLAPP: Does the 69 percent that we are discussing that consulted with a physician include from the CUSTOM study the pharmacist or

study personnel or is that just specific for physicians? I think the data said consulted with a physician. Did you mean physician or a healthcare professional as described here?

MR. HANSON: To clarify that, the study personnel on there was just an artifact of the clinical study and study personnel actually would mean pharmacist in the real world, so just replace the word "pharmacist" for study personnel.

DR. CLAPP: So when we were talking about that 69 percent that consulted with a healthcare professional, do you mean specifically a physician or are you saying physician/pharmacist?

MR. HANSON: The data from CUSTOM was 57 percent sought a physician and about 30 percent of the people interacted with the study personnel which was a mock pharmacist in the study.

DR. WOOD: No, but I don't think that is the answer she is getting at. 57 percent saw a physician at some time through the year but it might have been--

DR. CLAPP: No.

DR. WOOD: Is that not right?

MR. HANSON: Sometime within the course--the six-month course of the study.

DR. WOOD: That might have been with a broken ankle.

DR. CLAPP: Right.

DR. WOOD: Are we misunderstanding that? That was my understanding. So you are saying 57 percent of them saw them about this study? I don't think so.

MR. TIPPING: Can I have Slide 158 please? Just real quick because it gets right to the point.

DR. WOOD: There is an easy answer to give. Did they see a physician because of this study or did they see a physician for any--

[Slide.]

MR. TIPPING: 57 percent of the users in CUSTOM and, in this case, these are 57 percent of the users who saw a physician about Mevacor OTC, so it wasn't because they went because they feel and broke their ankle.

DR. CLAPP: When those 69 percent sought

help with making a decision--didn't I see 69 percent sought help in making the decision by consulting with a healthcare professional prior to purchasing the medication? Am I misrecalling?

MR. TIPPING: I am not recalling the 69 percent.

DR. CLAPP: Or needed more information? Let me ask you this. What percentage are you saying consulted with a physician to make their decision prior to purchasing the medication?

DR. WOOD: Or not purchasing.

DR. SCHAMBELAN: Purchasing or not purchasing. They might decide either way once they consulted the physician. I think that is the number we would like to know.

MR. TIPPING: There were 620 who did not consult with a physician of our 1,059 so it is about 430 something.

DR. SCHAMBELAN: And of the people who decided not to participate, is that based upon a physician's advice or was that their own decision?

MR. TIPPING: So you are talking about the

over 2,000 who didn't purchase and I think I would have to go back to the slide, but I believe 19 percent of that group specifically said that they had talked with a physician before making that decision.

DR. WOOD: Here is the question that Dr. Clapp was asking, I think, and I still don't think you have answered it. Are you telling us that 57 percent of the patients who were in that study consulted a physician about participating in the study because that is not what I understood you to say before and that is quite different from--I mean, that is a devastating number if that is the truth.

MR. TIPPING: 57 percent of the users had an interaction with a physician about Mevacor OTC.

DR. SCHAMBELAN: Those are the users.

MR. TIPPING: During the study.

DR. WOOD: All right. Do we know what percentage saw a physician for anything over that six months?

MR. TIPPING: No.

DR. WOOD: So went to their gynecologist or--we don't know that?

MR. TIPPING: I thought that is what that

57 percent was.

DR. WOOD: No; we were asking them specifically about interactions having to do with our product.

DR. WOOD: Any further discussion on this? Do you expect the general population will have this degree of physician interaction? Dr. Woolf? Try and do both at the same time because we are rolling along here.

DR. WOOLF: No, I do not expect the general population to have that kind of interaction without--the answer to that is no, both a. and b.

DR. BENOWITZ: For Part a., I abstain. I just don't have enough information to make any judgment about that. For Part b., I think that if we expand it to a physician or pharmacist or 1-800 number, I would say yes.

DR. BLASCHKE: Based on what we just heard, I think the number might go down in Part a.,

so I would probably answer no, that it will probably go down in terms of physician interaction. To 6 b., I would answer yes, I think that, again, with the change that Neal suggested.

DR. CARPENTER: No to both.

DR. PARKER: I would say unknown to the first and no to the second.

DR. FOLLMAN: I would say no to the first and the fact that we haven't really studied and we haven't done a CUSTOM study for this population, we think it doesn't have access to physicians, I would have to say no to the second.

DR. DAVIDOFF: I would say no and no.

DR. PATTEN: No to both.

DR. McCLUNG: No to the first and, unless we believe that interacting with physicians makes things be worse, then the answer to the second part is no.

DR. CLYBURN: No and no.

DR. MAKRIS: I would say no to both but I believe that there are probably some things that could be done to move towards a yes.

DR. CLAPP: No. No.

DR. SCHADE: No. Yes.

DR. TAYLOR: No to both.

DR. SCHAMBELAN: No to both.

DR. WOOD: An unknown, I think, to the first one and I would say no to the second one if what we just heard was really true, that 57 percent of the patients consulted a physician about the study which is not what I understood the data to show.

DR. TINETTI: I would say we don't have enough information for a., and no to b.

DR. WATTS: No to both.

DR. NEILL: Yes and no.

DR. WIERMAN: No and no.

MR. SCHULTZ: Unknown and no.

DR. FINCHAM: Yes and no.

DR. SNODGRASS: No and no.

DR. WOOD: Question No. 7; do the results regarding self-management--that is, user behavior after the initiation of treatment--raise any concerns about the safety and effective use--oh;

before we get to that, I promised we would come back to quickly list other exclusions that Dr. Parker and others had outlined, and Dr. Benowitz. We had alcohol, transplantation. Are there any others that we wanted to get on the record for that from the committee? A single word will suffice.

Then let's move on. No. 7; do the results regarding self-management--that is, user behavior after the initiation of treatment--raise any concerns about the safe and effective use of lovastatin 20 milligrams in the over-the-counter 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.

Discussion. Neal?

DR. BENOWITZ: I just want to go back to something that we have talked about on and off and that is some indication to the patient about potential benefits in absolute terms because, while I am totally supportive of the public-health benefit, I think someone needs to know that they

need to take a medicine at great cost for a long period of time for a relatively small individual benefit. I think that needs to be communicated effectively.

DR. WOOD: I agree with that. Any other discussions? Dr. Clapp?

DR. CLAPP: Is this for the target population that we are discussing?

DR. WOOD: I guess not. Well, maybe. I don't know. Do you have a comment? Make it anyway.

DR. CLAPP: I think, if it is for the very narrow focus of the target population, the small percent that self-selected correctly, then the answer would be different.

DR. GANLEY: No. For No. 7?

DR. WOOD: Yes.

DR. GANLEY: It is anyone who is in the study. So, whether you were the target population or not, it is still a measure of someone's behavior. So it is trying to get at that.

DR. WOOD: Could we make that--obviously,

there is always concerns. Charlie? Raise any concerns. Do you really want any concerns of any sort?

DR. GANLEY: Significant.

DR. WOOD: Significant concerns, maybe.

DR. GANLEY: Significant is fine.

DR. DAVIDOFF: I think if I had to single out any particularly significant concern, it would be with the first one with the monitoring of LDL-C because it seems to me that that could potentially be a really important way to help focus the therapy so that it was more efficacy rather than less.

I don't remember the exact numbers on follow up LDL cholesterols, but they were fairly good. I think it was in the range of 60, 70 percent, or something of the sort. But it seems to me that that certainly could be seen as the glass being at least a quarter empty and that that is something of a concern.

Related to that is the concern that we haven't heard at all and that is about the accuracy of cholesterol testing because there is a lot of

mention made of on-site and sort of bedside cholesterol testing. The last time I looked, the accuracy of that testing was quite variable. It might have improved since I last looked, but I think that that--throw that into the mix and you really do have a soft spot in the self-management issue.

DR. WOOD: Any other discussion? Neal?

DR. BENOWITZ: Something, just because of my research that I am curious about, and that is the smoking business. A lot of smokers stop and they relapse and they stop and they relapse. So there is sort of one risk factor that is flapping back and forth. I am just curious to know how one self-manages when one has a disappearing and reappearing risk factor.

DR. WOOD: You are the man. Tell us what you think, how you feel.

DR. BENOWITZ: I don't have an answer. I am just curious.

DR. WOOD: Well, then, I doubt that any of us do. Are we ready to vote on that? Then let's

start with Dr. Snodgrass.

DR. SNODGRASS: The way the question is worded, I will answer yes and then what are my concerns. It was 57 percent that had some sort of physician interaction. I think there are so many potential other illnesses, disorders, involved in the population that that is too low a number. That is one concern I have about this and that is why I answered yes.

DR. FINCHAM: Yes. And I have concerns about drug interactions that weren't picked up, weren't monitored, that there was no way to follow.

MR. SCHULTZ: Yes. And I am concerned with subsequent adequacy or frequency of the follow-up testing that would be needed if someone is going to really keep a close tabs on this.

DR. WIERMAN: Yes. And I am concerned that the study hasn't demonstrated that we are there yet in adequate monitoring for efficacy and safety long-term.

DR. NEILL: Yes. Inadequate access to healthcare for most patients makes this not doable

and the low benefit to patients who inappropriately self-select when they are at low risk makes this akin to giving them very expensive supplements when we have already heard are available to them, they are already using and aren't a good idea.

DR. WATTS: Yes. I agree with all the concerns that have been raised and am particularly concerned that that is going to be money spent for short-term, make you feel better that you are doing something but won't have any long-term benefit to the patient or to the population.

DR. TINETTI: I would say yes and concur with what has been said so far, and also add that there is no confidence that these people are going to recognize when they have new conditions that develop over time so they no longer meet criteria for over-the-counter.

DR. WOOD: I would say yes as well. We have spent a day and a half talking about concerns so it would be hard to answer that no, I think, at this stage.

DR. SCHAMBELAN: I would say yes and add

that the other features of the metabolic syndrome will continue to appear in this population. We will gain a pound or two a year and, if they are not paying attention to that, they are not going to get the same benefit that they otherwise would under a physician's care.

DR. TAYLOR: I would say yes because I think many patients will want a physician interaction. For some populations, they have no physician and, therefore, they won't get an LDL because they are not going to go and buy a self-testing kit. Those of the population that I see are lower income and, therefore, compliance will become an issue.

DR. SCHADE: Did we change the word "any" to "significant" in that sentence?

DR. WOOD: No; we did not, I don't think.

DR. SCHADE: Does the sentence say "any" or does it say--

DR. WOOD: It says, "any concerns about the safe and effective use."

DR. SCHADE: I don't know what I am voting

on. Does it say "raise significant concerns" or "raise any concerns?"

DR. WOOD: We didn't discuss what "significant" is so I voted actually just on what is written.

DR. SCHADE: The way, then, I would vote yes, if it is "any," and no if it is "significant."

DR. WOOD: Right. I probably would too, but I think--

DR. CLAPP: Yes. And many of the reasons have been discussed.

DR. MAKRIS: I would say yes. It is not so much that the study raised specific concerns in and of itself but, rather, that it wasn't of long enough duration and didn't really evaluate the long-term behavior of people to address whether or not these would be an issue.

DR. CLYBURN: Yes, for the reasons already stated.

DR. McCLUNG: Yes, for the reasons already stated.

DR. PATTEN: Yes, for reasons already

mentioned plus the fact that 270 of 356 people in the CUSTOM study got a new prescription during the study and I would be concerned that, if the use of statins was not on their medical record, they may neglect to tell their physician at the time they get a new script and that could present a hazard.

DR. DAVIDOFF: Yes, for many of the reasons already mentioned.

DR. FOLLMAN: Yes, for the reasons mentioned.

DR. PARKER: Yes, for the reasons mentioned.

DR. CARPENTER: Yes. Ditto.

DR. BLASCHKE: Yes, for the reasons mentioned.

DR. BENOWITZ: Yes, but I would like to make a pitch for pharmacist involvement because I think a lot of this could be dealt with if we really had a system more like the U.K. where we really had a pharmacist who was involved with the patient, who was supervising cholesterol measurements. So I think this is something that

could work but we need a better system. So I would just try to urge whoever can make these changes to think about those kind of changes.

DR. WOOLF: Yes, for the reasons enumerated before.

DR. WOOD: 23 yeses, 0 no's.

The final and critical questions; should Mevacor OTC be marketed OTC. I think we deleted, "for the proposed population;" is that right? So the question now reads, should Mevacor OTC be marketed OTC, period. Then we will get to these other ones in a moment.

Do we want to have discussion on that? So take that out, that last part.

DR. SCHAMBELAN: Could you clarify that? It would include all comers? The box would exist in the supermarket like Tylenol, you just go ahead and pick it up? Is that what you are asking us to vote on?

DR. WOOD: No. Just should it be marketed OTC under any circumstances.

DR. SCHAMBELAN: That is what I am saying.

DR. WOOD: No, no, no. Are there circumstances under which it could be marketed. I think that is the--

DR. SCHAMBELAN: How would we know what those circumstances are?

DR. WOOD: I will let the FDA answer that.

DR. ORLOFF: As proposed.

DR. SCHAMBELAN: That is for the targeted population, then.

DR. ORLOFF: But it is also with the box and what you have heard about and everything.

DR. SCHAMBELAN: As proposed. All right.

DR. ORLOFF: And if not, why not? What is lacking? What is missing? They have proposed something. Should it be approved or not?

DR. WOOD: Frank?

DR. DAVIDOFF: I just like to make a few comments in connection with the general question. I think it is very clear that there is obvious benefit to this drug. It is an amazingly effective drug in targeted therapies including secondary prevention. I understand the interest in moving

ahead to broaden the use to the primary-prevention dimension.

My thinking really started out very much strongly in favor of going on that direction. I mean, there have been times in my career when I thought the statins ought to be in the drinking water. But contrary to Dr. Cohen, my view has evolved in the opposite direction and I have gotten progressively more concerned as I looked at the evidence and got deeper in the subject. I think it does remain a very tricky question to decide.

I have three main concerns. The first is, as a number of people have mentioned, the efficacy for primary prevention, I would argue, is really not known. We just plain don't know what that efficacy would be in the actual over-the-counter setting. But what is almost certain is that it would be considerably lower than the figures that are being presented that are derived really directly from randomized trials which I think is not an appropriate extrapolation. So that is No. 1.

No. 2 is that primary prevention with statins is not cost effective, and I will come back to that in a moment. The third has to do with the

concerns about pregnancy which we have really heard a lot about.

On the efficacy question, it seems to me that the key issue here is not what happens to people's cholesterol level. That is a surrogate measure and I think everyone pretty much agrees that what really matters is the absolute risk reduction for cardiovascular events. Yet we haven't heard the information presented in terms of absolute risk reduction.

The closest we have come has been number needed to treat which is, as pointed out, the reciprocal of absolute risk reduction. The figure that has been presented by Merck is an NNT in the range of 35. You have to treat 35 people for six years to achieve a 3 percent reduction, absolute risk reduction, because that is the reciprocal of 35, roughly.

But I would raise substantial questions

about that absolute risk reduction for the following reasons. First, the baseline risk on which that NNT is based, I would argue, is unrealistic. We have already seen that very close to 50 percent of the CUSTOM users were taking low-dose aspirin. In fact, they showed another slide in which that 50 percent was amazingly consistent across all the studies, that, since we know that aspirin lowers absolute risk by about 30 percent, that means the baseline risk was not what was being assumed, as near as I can tell, but was actually somewhat lower.

If you do the numbers, and I think I did the math right, that means that the absolute risk reduction would go down to about 2-and-a-half percent, given the starting baseline risk.

I would also point out that only 40 percent of the CUSTOM users reached a goal of less than 130 milligrams percent of HDL cholesterol whereas, in the AFCAPS study, the rate of reaching that goal was 81 percent. So, to extrapolate from the AFCAPS numbers in the randomized controlled

setting to over-the-counter use seems to me to be not appropriate. In fact, I think you have to cut the efficacy by about half, roughly. So that gets you down to 1.25 percent absolute risk reduction given that lesser reaching of goal.

The third point is that compliance is an issue, as has been discussed. On about 65 percent of the expected doses were taken in CUSTOM in six months. The drop off, as we have seen from other studies, continues over the 12 months at least beyond that so that figures in the range of 25 to 50 percent adherence over the long term seem to be much more realistic. After all, as has been pointed out, there is no incentive to keep taking the drug because there is no symptom relief and there is disincentive to continue taking it because people are paying out of pocket.

In fact, in the AFCAPS study, 99 percent of the participants had taken 75 percent of their pills at the end of one year. That is way beyond what was true even in the six-months CUSTOM study.

So I would argue that, as a reasonably

conservative estimate, that drops the absolute risk reduction down from 1.25 percent down in the range of 0.6 which comes out to be a number needed to treat somewhere in the range of 100 to 200.

Now, having got that far in my thinking, I decided, well, that is still probably a meaningful benefit if you multiply that over many millions of people. That is not a trivial number of cardiovascular events prevented.

Part of the problem, though, is we really don't know, and, unfortunately, the opportunity hasn't been taken advantage of to find out. So, looked at that way, I think you could argue that going OTC statins would, in a sense, be a massive uncontrolled experiment. I just would hope that someone might actually do the study that gives us the data so that it wouldn't be an uncontrolled experiment.

Without that, I would see this as not a good model for how the FDA might move into the over-the-counter area of treating chronic diseases.

DR. WOOD: Let me try and present the

opposite view because I think that is an interesting perspective. You are saying sort of that we shouldn't approve something because the group at the lowest risk will get a relatively small benefit. So, to argue the counter view which is a sort of libertarian, I suppose, view, that sounds awfully paternalistic. I mean, there are clearly people who are going to derive substantial benefit--well, who are going to derive benefit within the group for whom this therapy is targeted.

One of the attractions of over-the-counter availability is that individuals have the right and opportunity to make that judgement of what risk benefit and what cost benefit specifically they are prepared to assume. It seems to me that there is a difference between, for instance, deciding whether a health plan is going to pay for something and deciding whether a drug should be available to individuals to make that decision for themselves.

So, while it is fine to go through multiple iterations saying, well, people with an LDL of only fill-in-the-blank take this, the

benefit will only be X. For people with an LDL that is substantially higher than that and choose to take it and choose to pay for it themselves and decide that that benefit is worth it to them, that is their decision which is a different paradigm from society paying for it out of their healthcare plan.

So it does seem to me that that analysis, while the usual one we do, number needed to treat of whatever, is one that is applied to a population where the population, as a whole, is paying for it.

Here, we are in a different situation. Individuals are making that judgment and in a way that we make that judgment every day. Some people decide to put smoke detectors in their homes and some decide not, or whatever the analysis is.

So I am sort of left uncomfortable, I must say, listening to that analysis, saying, well, we are not going to approve a drug for over-the-counter use because some patients who might derive relatively little benefit would take it and, for them, it might not, in our view, be

worthwhile but, on the other hand, in their view, it might be, and, similarly, there are other patients out there who might derive benefit but they should not have the opportunity to do that.

It is sort of like if you look at where physicians LDL is, it is probably at least as low as the guidelines, probably down at 70 for many if they are on statin. So I am not sure that is the right analysis.

DR. DAVIDOFF: You didn't let me finish.

DR. WOOD: Okay. Sorry; I thought I had.

DR. DAVIDOFF: I am hoping that what I have to say that I didn't get to say yet will, perhaps, make a difference in your view because I would continue by saying that, as the potential benefit shrinks and, again, as has already been pointed out, the relative balance between benefits and risks also shift. It shifts in the direction of being a bit more concerned of, are we getting the bang for buck relative to the potential risks.

I think, if the only issue is is having to treat 100 people for six years in the face of the

apparent relatively rare serious side effects, I would agree with you, that I think that that is probably in favor of going ahead.

But I haven't finished. The other issue that I think is highly relevant is the issue of cost effectiveness. By that, I am not talking again about just purely financial and economic issues but cost effectiveness which is a kind of a bridging concept between resource use and clinical effectiveness.

The basis of my thinking about that was an article that was published in Annals of Internal Medicine in the Year 2000. The lead author is Prosser but the senior author was Milt Weinstein who wrote the book on cost effectiveness. The article is Cost Effectiveness of Cholesterol Lowering Therapy According to Selected Patient Characteristics.

The reason that I think that that is relevant is not because I want to focus on dollars, per se, but on this ratio of cost effectiveness. Their conclusion was, after looking at extensively

across various categories of age, gender and other risk factors, was that, in their words, "Primary prevention is not cost effective. It costs anywhere from $62,000 to $1.4 million per quality-adjusted life year for primary prevention," depending on which group you are looking at.

In contrast, and this is the important point, the cost effectiveness for secondary prevention, which is effectively what happens in the prescription situation, is $1,800 to $40,000. So, in effect, the cost effectiveness of primary prevention versus secondary prevention is between 1 and 2 orders of magnitude less cost effective.

Those calculations are based on efficacy from randomized trials not from the efficacy of the much less efficient situation that would occur in over-the-counter treatment, $50,000 per quality-adjusted life years, a commonly used benchmark for cost effectiveness which is why they came to the conclusion they did.

I think it is also helpful to consider, by way of comparison, the cost effectiveness of

something much more tangible and that is--the example they use is single-vessel angioplasty for severe angina, the cost effectiveness of which is $10,000 per quality-adjusted life year.

So I think that that does have to be weighted into the balance. Is this kind of expenditure, whether it is out of pocket or from insurance carriers, it is still money being spent for healthcare. Is that a good use of money in this area of healthcare. I think that does have to be weighed into the equation.

DR. SCHWARTZ: Dr. Wood, I am Sandy Schwartz from the University of Pennsylvania. We didn't talk about cost effectiveness at all because we were told cost wasn't going to be an issue. But there are a couple of important--

DR. WOOD: I think we are going to have to just keep going at this stage because we are getting close to the end. We haven't presented that. But we are close to the time out so I am going to have to cut you off.

DR. WATTS: I want to make two points.

One is that it has been alluded to but not really focused on that the leap from prescription status to over-the-counter status is a big one. It seems awfully attractive to have an intermediate category as they do in the U.K. and I would urge the agency to explore some possibility of creating a behind-the-counter, because I would feel much more comfortable having these discussions if there was some sort of sea-wall between next step and the general public.

DR. FINCHAM: I couldn't agree more. My vote would be completely different if that was the case.

DR. WATTS: I don't think my vote would be different because I am concerned, too, and the second point to make is that this sets a precedent that would then need to extend to other drugs in this class and other drugs for the management of chronic silent diseases.

I am not comfortable at this point, certainly not with the data that has been presented, but it is hard for me to conceive of

adequate data that I would feel comfortable in looking at antihypertensives for over-the-counter use, even though blood pressure assessment is probably more widely available than cholesterol testing, or for anti-diabetic drugs for over-the-counter use, even though self-blood-glucose testing is available and accurate.

I am concerned that the precedent to move this to a non-prescription category, be it a behind the counter or in front of the counter, has really serious ramifications that go beyond the decision for this particular compound.

DR. WOOD: Any other discussion? Are we ready to vote on this? I have forgotten where we started last time.

MR. SCHULTZ: If I might add something.

DR. WOOD: I'm sorry. Dr. Schultz? I beg your pardon.

MR. SCHULTZ: Along the lines of the last speaker, I would like to say if there is any way for this committee to offer that suggestion to FDA

as part of our deliberation, I think it would be a very fine thing to do.

DR. WOOD: Okay. Thanks. I have forgotten which side we started on last time. So we will start with Dr. Woolf?

DR. WOOLF: I vote no. I don't think that the support system is out there for patients, potential patients, to make an adequate assessment. We have no data that, even if there were pharmacist in place, that that would be an adequate backup, not to mention the fact that there would be lots of patients who could be buying the product when the pharmacist is no longer on site. What does that person do? Does that get folded up and taken away? Does that person buy the product and come back to speak to the pharmacist another time or not speak to them?

So, for all the reasons that we have discussed over the last two hours, plus I don't think that the backup system to make an informed decision is there. So I vote no.

DR. BENOWITZ: Let me say first that I am

in favor, in general, of the idea of nonprescription lovastatin, however, not for the system as proposed. I see five things that need to be dealt with specifically.

One, I think there needs to be an accurate benefit description so people can really make judgments about if they are going to buy it, which I agree with you, Alastair, that people should have the right to do that. They should know what the benefits are that they are paying for.

I think there needs to be better protection in terms of pregnancy risk. I think there really needs to be better care available in terms of pharmacist care or someone to ensure that there is better follow up.

I think there needs to be an interaction between the FDA and whoever regulates marketing so that it is marketed in a fair and balanced way. I think we need to be sure that when generic OTC's come, that they are brought into the same system.

DR. WOOD: So is that a yes or a no?

DR. BENOWITZ: It is a no.

DR. BLASCHKE: Well, to balance that, I feel exactly the same way as Neal does but, since we have to give a categorical answer, I will say a

categorical yes with all of the caveats that Neal has just mentioned. My concerns are exactly the same, the pregnancy issue, the issue of what the patient really knows about what he or she is buying in terms of the benefits, the importance of the involvement of the pharmacist, et cetera. But, as a categorical answer, I will say yes.

DR. CARPENTER: I say no. I do agree with Neal's comments as well. I would welcome and would push exploration for a p-level designation or something analogous to the p-level designation in the U.K. I think it is worth mentioning that this is an extremely difficult question at hand because, unlike most of our tasks in these committees, we are not really simply evaluating the product here. We are being asked to deal with an entire policy and philosophy of healthcare.

I think the no's are couched in the fact that the way this whole system is packaged for us

at present is quite uncomfortable for the reasons alluded to.

DR. PARKER: No, based on the fact that I don't think the presented studies support that people can adequately self-select and manage without an informed intermediary and also because I don't feel that the current proposed labeling fits with the FDA regulation that it be likely to be read and understood by the ordinary individual including individuals of low comprehension.

My third concern relates to the cat out of the box once marketing takes over.

DR. FOLLMAN: I would vote no. My main concern has to do with the fact that I don't view we have had really evidence in terms of events benefits done for this. The studies that have been done have compared statins to nothing. I think the proper comparison is statins in a prescriptions, statins in a over-the-counter world. I just don't know which way that would come out. I don't have any evidence. So that is my main reason for voting no.

I have a few comments on the label. One is that I think it is important to require annual cholesterol testing, at least put that on the

label. The label also suggests that those who don't reach goal at 6 weeks should just stop taking Mevacor and, by the way, also see a physician. I think it is important that they should see a physician if they start because the treatment isn't effective enough for them.

And, as has been mentioned, I think, the fact that the CUSTOM study had 10 percent of the women less than 44 years of age is also of concern.

DR. DAVIDOFF: I would say no. But I would also say that I think Merck deserves a huge amount of credit for moving this issue forward or at least trying to do so. I hope that they don't give up their efforts and also that the FDA joins in the effort to try to actually develop an OTC approach that is more demonstrably effective and cost effective and then all measures that could move it in that direction ought to be looked into including behind-the-counter kind of dispensing,

improved labeling, et cetera because I think it is the right thing to do. But I don't think we are there yet.

DR. PATTEN: I vote no. This is based on results from the CUSTOM study that have already been discussed. It is also based on the fact that the way our healthcare system is currently configured, we do not have the option that the British have. I think that is an option that should be considered. I don't that the idea of pharmacy-care OTC that we heard addressed this morning really gets at that issue. There are many labeling problems that have already been mentioned. One that passed me by until just a few minutes ago; if, indeed, age is the first criterion that people should use to decide if this medication is appropriate or not, then age should be on the front of the package. If you are a female, 55 or over, if you are a male, 45 or over, should be right there for people to see.

DR. McCLUNG: No, but not because of the concern about the effectiveness of the drug, but

because of the strategy that is outlined, my uncertainty about the ability of prospective patients to adequately assess their needs for choosing to take the therapy.

Secondly for the reasons outlined eloquently by Dr. Davidoff about the concern about low-risk patients being treated. Lastly, the uncertainty about whether this strategy is actually better than a physician-based approach that has the same amount of educational and motivational support that this program would have from the marketing angle.

DR. CLYBURN: No. I have no doubts that statins are safe and effective within the target population. My concerns are more with the self-selection process and I would support a behind-the-counter, over-the-counter, option.

DR. MAKRIS: No, based upon concerns about the current proposal as it was presented. I think there are a lot of opportunities to improve it or to move forward in some of the directions that have been outlined by this group today. I see that

there is a real need for this type of marketing, perhaps in the future, but I don't believe that this particular proposal addresses all of the concerns that have been raised.

DR. CLAPP: I think that the behind-the-counter option would be a perfect solution to this dilemma. Mevacor seems to be crucial in heart health and a great drug for it. But, unfortunately, because of the nature of the marketing, I think that it puts the risk:benefit--it shifts the risk:benefit ratio with the other considerations that we have described.

But, as Dr. McClung mentioned, I think if Merck could give the same level of aggressive marketing to physicians for re-education for them and, perhaps, pose Merck 20 milligrams in the same realm as a vitamin or aspirin or something that is a kind of salubrious solution that doesn't seem as pharmacological to the patient consumer as another prescription medicine that is 40 milligrams, perhaps posing it as an optional medicine for people because, then, they can conceive that they

made a choice.

You could, perhaps, have the same public-health benefit to the consumer and then have the ability to target those who need more than the 20 milligrams.

So I applaud Merck for their attempts at putting this forward and I see that the CUSTOM study was a good attempt. It gave us a lot of information as to how to perceive and, perhaps, better construe a study for the future. I am hoping that they won't drop this effort and I am hoping that the FDA will have some solution for the future of changing access to over-the-counter medicines to behind-the-counter, as they do in U.K.

But I also hope that Merck will consider aggressive physician education for this matter because I think, in the interim, the public would benefit from the 20-milligram Mevacor.

DR. SCHADE: I vote yes.

DR. WOOD: Hang on. We didn't get a vote. Did we get a vote?

DR. CLAPP: No.

DR. WOOD: Thank you.

DR. SCHADE: I vote yes for the overriding reason that there are millions of Americans in this

country with no health insurance and absolutely no access to a statin except, of course, to fly to Britain. I think that these people deserve the right to lower their risk and prevent cardiovascular disease. Until we provide something over-the-counter at a significantly reduced price and not having to get a physician's prescription, we are going to continue to have this huge burden, particularly in the uninsured. I think there is an overwhelming urge, or should be an overwhelming movement, to make absolutely important medications available to noninsured individuals in this country because, as I think everybody knows, the healthcare system is not going to be fixed by tomorrow.

So I vote yes.

DR. TAYLOR: I would vote no. I think we have some serious infrastructure problems in implementing the current proposal. I do think we have to do something about the gap in those

individuals being treated. I do think that there are a group of individuals that do need more health-professional intervention and they would not be able to operate effectively in this system.

Perhaps, integrating it into a more systemic way into the healthcare system, systems that are being proposed for the future might be a way to do that. But this proposal, I think, does not do it. Pharmacy behind-the-counter would, however, generate some enthusiasm.

DR. SCHAMBELAN: I vote no for many of the reasons that have just been articulated, particularly around the issue of approval as proposed. I don't think this meets the criteria, at least to satisfy me. I also feel that the idea of a behind-the-counter access such as will be studied in the U.K. might well be an answer.

I think Dr. Follman asked for a city-by-city comparison. I think we may have a chance for a country-by-country comparison to see how this does in an OTC setting and, maybe in a year or so, we will have some data that we can look

at.

DR. WOOD: I vote yes on the basis that the drug is safe and effective for use without the intervention of a doctor in the target population that it was designed to look at. I am less impressed with the arguments about cost effectiveness in that I think people should have the right to spend their money as they wish.

They do need to have a clear understanding of the likely benefit that they, themselves, may derive from the product and that currently isn't on the label but should be and the opportunity to calculate that should be there.

The reality is that the vast majority of these patients we receiving no therapy right now and should be. I think the idea that we should deny these patients therapy is disturbing to me. So I would also agree with Neal Benowitz and Terry Blaschke and what Dr. Schade said, and not repeat it again, but even though one of them voted no, I think these are arguments for approving the drug for over-the-counter use.

DR. TINETTI: I vote no. I am very strongly supportive of moving in the direction of self-management but I don't think we have heard,

over the last two days, the evidence to support that the overall benefit either to the population or the individuals will be better with it over-the-counter than its present situation. I encourage Merck and the FDA to move towards the kind of study and evidence that can help address that question because I think it is a very important one.

DR. WATTS: I vote no. I am convinced that Mevacor 20 milligrams is safe and effective in the target population but it is a moving target and I am not convinced that patients who fall outside that target are properly channeled to where they should be if they fail to reach goal or new conditions develop. I am not at all convinced that patients can self-select for the target population, that considerable support from health professionals is needed and that is why it is a prescription drug.

DR. NEILL: I vote no. The answer to the lack of insured patients in this country isn't a piecemeal thing like this. It has to be much more global. In addition, while I respect the right of people to be able to choose to spend their money the way that they wish to, in fact, for the

fraction that have some insurance in this country, what we are talking about is how my tax dollars are going to be spent. That is going to be altered dramatically by a choice like this not just in terms of how or whether cholesterol-lowering medicines become available over-the-counter but how we manage and defined OTC conditions.

We have spent very little time talking around the edges of that but that is a huge, huge issue that should not be discussed sideways but directly.

DR. WIERMAN: I vote no.

MR. SCHULTZ: I vote no on the basis that self-selection does not produce a likelihood of continued use if there isn't some intervention with professional medical personnel and should be that

way.

DR. FINCHAM: I vote no. The Institute of Medicine, crossing the quality chasm that was referred to in the sponsor's document, they talk about communication, coordination and integration of care on Page 49. That would be missing in this process as it is proposed in the United States.

The British system would remove and questions and qualms I have about this being significant. I think it is a tragedy. You don't have to fly to the U.K. You can drive to Nogales or any other city in Mexico and buy this easily without any of this.

So I encourage the FDA and I certainly encourage Merck to continue this process but I have to vote no now.

DR. SNODGRASS: I vote no. Many of the reasons have already been stated quite well by many others. I would strongly encourage Merck as well as working with the FDA but continue to address this issue. It is clear that it has some real potential on a lot of levels. But I just think the

overall benefit:risk ratio is still not there.

I would like to make one small statement about the pharmacy issue. I think that is a good idea and it could advance this considerably. But, even that, I think, in the United States context, would have to be looked at very carefully with regard to numbers of pharmacists, the depth and quality of their training to deal with this with regard to the actual patient benefit.

DR. WOOD: Great. So the vote is 20 no and 3 yes. I think we have answered all the other questions so I don't think we need to proceed from that. It is 3 o'clock and I think that is the end. Oh, wait.

DR. MEYER: I simply wanted to thank the committee for the two days. I think this has been a very thoughtful discussion. We have gotten a lot out of it from your participation and thank you very much.

[Whereupon, at 3:00 p.m., the meeting was adjourned.]

- - -