you're correct that we did not do that in the sort of wild-world setting where they are completely on their own.

That would have been very hard to follow them as to what they did and that kind of a design might actually be better done post-marketing.

But the trial that we did, they were not given appointments to come back. They were not given a lot of specific instructions on what to do, but they were given an eight-week supply of drug and told when you need a new supply come back to the site and they did that on their own in high proportions and got their lipids tested. That's the extent of the data that we have available.

CHAIRMAN BRASS: But following up on that, it's my understanding that in most of the studies, even the patients who said my cholesterol is between 200 and 240, when they were tested, less than half of them were actually in that range. Is that correct?

DR. LAROUCHE: You're asking me about the accuracy of their cholesterol knowledge?

CHAIRMAN BRASS: Yes. So when they responded on the self-selection portion of the study, is your cholesterol between 200 and 240, they said yes, then when you measured it, less than half of them

were?

DR. LAROUCHE: No, it was 56 percent in one trial and 61 in the other trial, of those people who thought they were between 200 and 240. The numbers were much more accurate when they were above 240.

There were about 88 percent who were correct. We're not expecting people to have totally accurate recall. We are actually expecting them to check their cholesterols before they start that, whether they do that in a doctor's office or in one of the community-based settings, because that's why they would have an incentive to continue treatment.

CHAIRMAN BRASS: I thought in study 076, of the 3,500 patients who got their cholesterol tested after being potentially qualified by everybody, 2,800 of them were not in the range.

DR. LAROUCHE: This is a slide from study 76 which is the best data we have for assessing their accuracy.

We asked them on the questionnaire what they thought their cholesterol range was, and of those people who felt they knew their range and it was within the OTC range of 200 to 240, 56 percent were correct and 40 percent were incorrect and their values

were above the 240 in actuality, though thought it was between.

And of those people who were above 240, 88 percent of them were correct. And the top figure, the 56 percent, is pretty well confirmed by a similar assessment done in the other study.

CHAIRMAN BRASS: But when you say plus or minus ten, does that mean you extended the range to 190 to 250?

DR. LAROUCHE: Right. We said that if they thought their cholesterol was between 200 and 240, but it measured within that little broader window, because we figured there was some wiggle room for variability.

CHAIRMAN BRASS: Okay. Again, part of this comes back to the selection point.

DR. SEGAL: Excuse me, may I just make a comment?

CHAIRMAN BRASS: Okay.

DR. SEGAL: In 081, the group with over 240 milligrams per deciliter cholesterol self-selected incorrectly with regard to cholesterol, about 46 percent of the time.

CHAIRMAN BRASS: So whether the number is 46, 56, to the degree that self-selection of this

range is important, to the degree it's important, and I understand it may not be if you're greater than 240, but let's just say to the degree it's important and to the degree the compliance with that label is important, I think the studies demonstrate emphatically that they cannot self-select for the reasons identified.

Now whether that nonselection is important or not, you can discuss. But I think clearly the data shows that patients do not self-select by the criteria on that label.

We can debate whether those are strict criteria, guidelines, whether there's a risk of being wrong, but I think the issue is that they do not adequately self-select. The issue is whether that matters a great deal or not in it's actual OTC use.

Go ahead, I guess I interrupted you.

DR. NEILL: Actually, I was going to move on to patient monitoring now because I still haven't heard any data that was collected to evaluate the ability of consumers to evaluate response to treatment.

The sponsor has evaluated response to treatment, but the question that I'm being asked to address is whether the consumers have the ability to

evaluate response to treatment? And to help me answer that, I feel like I need to know, what is the consumer's understanding of the expected result? How did they measure their lipid profile in vivo, not in the study?

You don't need to address that issue again if you don't like, but I don't have any data about how patients, how well or how poorly they present back to my office, or to a pharmacy community-based setting to do this.

And even if I understand that they do it 100 percent to have their lipids checked, I don't have any data that informs me about their ability to evaluate response to treatment.

DR. SLATER: Okay, let me try. There's a lot of questions involved in that. They're given a card, if you looked in the privileged information that you were given, and they're asked on that card at various intervals to fill in what their level is.

We did not attempt to study the question that you're asking. We could easily if you wanted. They are encouraged to communicate that information back to their physician.

That's, at this point, where we are at in terms of this paradigm. We clearly could work more on

the compliance side. As I told you earlier, our primary focus here was at the front end, namely at the self-selection.

To get to the issue of cholesterol recall, and I don't know if Dr. Brass, if you're going to there or not. This again, is sort of more of a survey of what people recall. The vision here is if patients --

DR. NEILL: I'm going to interrupt briefly because using the card, I want to go back to this paradigm that exists so far. I guess not what I'm asking you is did something like that exist, but rather how well do patients understand it and use and --

DR. SLATER: We have to look. We haven't looked.

DR. NEILL: Got it.

DR. SLATER: The second point regarding recall of cholesterol. You saw the little test kit this morning. I don't wish to endorse any particular brand, and nor did we intend to endorse any particular brand of testing, but the presumption here would be, and you say that you're not aware of how widespread it really is, but the presumption is that were this medicine to become available, were people to avail

themselves, they would also have the opportunity to get the tests done right at the moment in case they think they're okay for it, as a double check, as a recent check, as an up-to-date check in addition to being asked to call their physician if they know they've had a recent test in the last year, but they don't remember their number, again they are being encouraged to call and recover that number.

So we're not trying to ask people to wing it and I don't want the Committee again to get carried away that we're asking them to rely on memory, because as we all get older I'm not so sure how good that is.

DR. SEGAL: I'd like to make a comment to respond to you. The way I understood the trials, the actual use trials, was that there really were no treatment goals conveyed to the consumer. The concept was, if you take lovastatin, your cholesterol might go down, but there was no number for how far down it might go.

There was the concept that cholesterol is bad and people who have high cholesterol get sick, but there was no conferring of information to the consumer about what they would need to do with that range of cholesterol in these studies 200 to 240, how long they would need to take this medicine to keep from getting

a heart attack or a stroke or perhaps avoid peripheral vascular disease.

So, somebody could have taken, with lovastatin, they could have taken 10 milligrams and had a cholesterol of 240 and an LDL of 180 and maybe their cholesterol would have gone down to 220, maybe their LDL could have gone to, pick a number, somewhere, 150, and they would not have understood from the way these trials were defined, that that might not be where they needed to be if they were a smoker or if they had a low HDL.

So there really was no treatment goal defined as far as I could discern from these trials.

CHAIRMAN BRASS: Dr. Clark.

DR. CLARK: Yes. One point of the question, I think I ought to agree with your last two comments in that if the entry points for treatment are pretty clearly defined, but if the entry point is based on a number, then the patients will need to know what they are seeking to achieve in terms of their goal so that when they get a follow-up they know whether or not the medication they are taking has had an effect and what to do about it.

The other though, I would ask perhaps for a comment for the role of the physician in this

because there is a discordance in terms of what is being recommended to the patients about taking a drug therapy and what is contained in current guidelines for drug therapy that physicians are likely to be following.

These recommendations may be fine, but if the physician is following current guidelines that maybe contain, either from NCEP or their managed care group, and a patient goes to them, there's a great likelihood of being told that the patient may not even need drug therapy because current recommendations don't recommend drug therapy for these patients, and I think that potential for confusion needs to be dealt with up front so that the physician and the patient are not getting different messages.

CHAIRMAN BRASS: Yes. I'd just like to follow up. We heard that the lovastatin prescription label has been modified to incorporate the primary prevention information from AFCAPS and I think one of the issues, following up what you've said, is acknowledging that physicians can do this better using dose titration, monitoring, and intensive intervention.

I think we have to understand that we're on a learning curve for the profession, as you've

alluded to. Not that I'm going to be the defender of medical care in the United States, but much of the primary prevention data has only come out in the past couple of years and to see that beginning to impact on prescription utilization in a variety of settings, I think you're just beginning to see the impact on.

Just like it took many years for secondary prevention to reach a nonoptimal, but reasonably high level that continues to be developed in special populations.

The National Myocardial Infarct Registry continues to show increases in use of statins for secondary prevention and I think the timing of how we look at what the behavior of the medical community is, is a lagging indicator because much of the primary prevention information is relatively new on the scale of our ability to monitor behaviors. You had a comment?

DR. TAMBORLANE: I think you slipped it in, I just want to highlight this issue on the labeling about how much information is provided to the consumer and the duration of therapy that's required. That this is in fact lifelong therapy. This is not just take it for Christmas dinner. And I don't remember hearing anything about that information being

provided in the label.

CHAIRMAN BRASS: Other comments?

DR. SEGAL: That information was not in the label.

DR. DONALD UDEN: Is it truly lifelong therapy if in fact somebody --

DR. HEMWALL: Excuse me, I just wanted to say, we do have the information in our inserts and our packaging and in all the materials. This is a continuous therapy, that one does not take it intermittently.

DR. DONALD UDEN: Is it truly lifelong therapy if somebody has a total cholesterol of 220 and falls in that range, and gets the religion of diet and exercise.

It then is not necessarily lifelong therapy, and so if they do that, there would have to be a point in time where they take a drug holiday to see what their cholesterol is off of therapy.

CHAIRMAN BRASS: Dr. Neill.

DR. NEILL: The corollary to that is the patient's age and other competing co-morbidities arise.

For example, a diagnosis of cancer or progression of another chronic disease, which sets a

horizon shorter than an expected adverse event from cardiovascular disease, it would be much more difficult to show benefit.

But that's true for the prescription product and for many of the other chronic conditions that we treat. And it's not really directly related I think to the selection process or this question four that we're talking about. It is very important, but not to question four.

CHAIRMAN BRASS: Dr. Katz, would you like a vote on this, or would is that discussion adequate for that point? Okay.

The next is a mirror-image discussion, though we managed to get to letter G, related to the safety issues concerning 10 milligrams.

Specifically, in the OTC setting, the ability of the consumer to identify adverse reactions, ability of the consumer to monitor hepatic safety, including the need for hepatic transaminases, the need for and ability to identify and avoid interacting drugs, the likelihood of use of lovastatin at higher than recommended doses, the ability of women who are pregnant or are likely to become to appropriately avoid use, the need for the physician or other healthcare professionals in the safe treatment, the

capacity of the proposed label to direct consumers in the safe use.

Open for discussion. Yes, right Katz.

DR. KATZ: We've had more discussion. Can you back to question four and actually get a vote?

CHAIRMAN BRASS: You would like a vote on number four? Just on the global question or on each individual piece?

DR. KATZ: On the global question.

CHAIRMAN BRASS: So let me read number four again for a vote.

Assuming as an indication for the use of lovastatin 10 milligrams in the proposed target population could be justified based on an expectation of clinical benefit, has the sponsor adequately demonstrated that consumers can achieve such a clinical benefit in an OTC setting?

All who believe that has been demonstrated, please raise your hand and vote yes.

All those who feel it has not been demonstrated, please raise your hand and vote no.

DR. TITUS: Thirteen noes.

CHAIRMAN BRASS: Abstentions?

So, 0 yeses, 13 noes.

Discussion on the safety issue. Let me

begin by just highlighting some things that came up earlier. I think that the issue of avoiding interacting drugs is extremely problematic trying to list individual drugs and perhaps as was suggested by one of my colleagues, the more blanket statement, if you're taking any prescription drug do not use, may be a more effective warning.

Let me also say that I am extremely concerned about whenever we are labeling these OTC studies as actual use study, they are in fact still much more intensively monitored than actual consumer use in the real world, in my opinion, ever is.

And that I think it's extremely difficult to extrapolate that kind of experience even with the relative numbers that were shown here today to what the patterns of consumer use and understanding will actually be, so that the likelihood of a consumer who is already on a lipid-lowering drug, taking the drug, is unknown.

That just because under intensive, relatively intensive monitoring by a physician in the prescription setting, that 10 milligrams has demonstrated an outstanding safety profile as we previously voted on.

I do not know how to extrapolate that

experience to how consumers will actually use the product over the counter given that we have concerns expressed that there are higher risk situations. We don't know how much higher risk those situations are, but have heard mention of them, and I don't think we have any data or reassurance from the "actual use studies" that have been presented, how many consumers in those high-risk groups will actually be exposed to the statins if permitted to be used over the counter.

And finally, I remain with my hypothetical concern that since healthcare providers can do this better, how many patients, and I view this as a safety issue because it's avoiding optimal therapy, how many patients will not seek a healthcare provider because they think they are being adequately treated by an over-the-counter product? And I remain concerned about that as a safety issue. Other comments? Yes.

DR. EDWARD KRENZELOK: I don't think that I have the same concerns about safety that you've expressed. Again, as the sponsor has demonstrated, there are 24 million human-years of use and I think we have to look at actual experiential information.

Granted, spontaneous reporting is not the best obviously. There is not active surveillance going on. But it seems like there is a more than

adequate safety profile for this particular substance and I think this may be one of those situations where we indeed can extrapolate from clinical use and give it a fairly clean bill of health from that standpoint.

CHAIRMAN BRASS: So, for example, you would be confident that the likelihood of a patient on erythromycin taking OTC lovastatin is not higher than prescription?

DR. EDWARD KRENZELOK: I think I'd feel relatively comfortable with that, and for the most part that occurs across the spectrum of all drugs.

I don't think consumers understand what they take and it's clear that they probably don't understand what they take in combination with lovastatin either. And there hasn't been an inordinate number of adverse events.

CHAIRMAN BRASS: Yes.

DR. ELASHOFF: I have a concern about two of them. One is, it seems to me that those who have cholesterol higher than is specified on the package are fairly likely to take two or three times the dose because obviously if this wasn't quite enough for that, you take more.

The other issue that I'm concerned about is in the prescription setting, is it routinely

prescribed for women who are pregnant or likely to become so, and if not, then we really don't have any information about safety in that population?

CHAIRMAN BRASS: I don't know if sponsor wants to respond to the pregnancy issue. It's clearly not routinely used. There was some safety data presented in the materials distributed based on your experience. I don't know if you want to add anything to that.

DR. HEMWALL: Well, typically these drugs are not given to pregnant women because there is no benefit to be had in a women who is pregnant to carry on with that product during that short period of pregnancy.

If they have a hypercholesterolemia that requires that sort of treatment, they interrupt the treatment. We don't have that much experience in pregnant women for that reason and like all OTC drugs, this one as well, would be warned against using in pregnant women.

CHAIRMAN BRASS: Dr. Johnson.

DR. JULIE JOHNSON: If I can just run down this little list?

CHAIRMAN BRASS: Feel free.

DR. JULIE JOHNSON: The ability to

identify adverse reactions, I think most importantly that would be the myalgias or myopathy, and while I don't think they demonstrated that, that's probably because there wasn't much observed. I think that it's reasonable that a patient could identify that, although I'm a little concerned about the placement of that warning in the package insert. It's under the don't use with the following medicines warning, which implies that you could only get that if you're taking these medicines, which I think could make people who aren't taking any of those medicines ignore that warning.

So I think that that would need to be a separate warning on the label. But I do think that consumers could identify that. I don't believe there is a need, and I think that was well documented to monitor the hepatic transaminases.

The ability to avoid interacting drugs, I agree that it may not be logical to have a specific list since the list is obviously changing. I'm not sure that I agree that it should say if you're on any prescription drug don't take this, but rather if you are taking any prescription drug please consult your doctor or pharmacist to determine whether this is a safe product in you.

In terms of the pregnancy issue, I think your data pretty well documented with the information that you have, there doesn't appear to be risk should a pregnant woman be exposed.

CHAIRMAN BRASS: If I could just follow up on the myopathy rhabdo issue. Do either sponsor or the agency have, from the spontaneous reporting, the distribution by year, of those reports?

And what I'm wondering about, I'm wondering if people have stopped reporting rhabdo and myopathy since it is on the label as an adverse event?

Experience with adverse event reporting often is that the reporting decreases over time, particularly for an adverse event that is on the label.

And when we talk about the denominator of 24 million, or whatever that number was, I'm wondering if that is skewing because people are not reporting the myopathy anymore into the spontaneous reporting database. And I know in our setting we don't for example. And I know we've seen myopathies and we've never reported it.

DR. KORN: We have a distribution of overall number of spontaneous reports per year which of course peaked around early 1990s and has gone on

since then. We do not have it broken down specifically for myopathy.

CHAIRMAN BRASS: So it's quite likely that the myopathy follows a similar pattern, so that the true denominator might be really only the experience in the first few years, not the full 13 years of experience, hypothetically?

DR. KORN: Yes, that's true.

CHAIRMAN BRASS: Dr. Temple.

DR. ROBERT TEMPLE: There's a presumption that that's so. This observation was made by someone named Weber a long time ago and it's called the Weber curve, that reports of any given reaction drop off after about three years.

It has to be noted though that at the very same time we've intensely simulated reports, so that whereas we had 20,000 a year a decade or so ago, we now have 300,000, so the net effect of all that is hard to know.

For what it's worth, when mibefradil came out, we got seven reports of rhabdomyolysis associated with simvastatin and it in about two months. So people can be provoked to report.

CHAIRMAN BRASS: Yes, Dr. Parks.

DR. PARKS: Another thing I wanted to add

to that with respect to reporting rates, often a labeled event may not be something that clinicians may report because they are under the assumption that this is something that is already known and toxicity is already known, and therefore it does not need to be brought to the attention of the drug company or to the FDA.

CHAIRMAN BRASS: Yes.

DR. LUKERT: I'm concerned about two other groups of patients. I don't think we have a way of estimating how many people this would affect, but I'm concerned about the patient who's hypercholesterolemic because they are hypothyroid for example.

We can't assume that all patients who have a modestly elevated cholesterol just follow the primary category. And I say this because I see a number of laboratory people who have the ability to check their own cholesterol and do and start starving themselves and lo and behold, they're hypothyroid and finally get discovered.

The other is the group of "worried well" who are likely to take this drug, even with a normal cholesterol or even perhaps a rather low HDL. The same group of people who take all kinds of herbs and supplements, would probably like to add this to their

armamentarium.

CHAIRMAN BRASS: Dr. Uden.

DR. DONALD UDEN: Yes. I want to follow up on the comment made earlier about those people who have cholesterols who are on the OTC from the 076 and 081 studies. Approximately half of them had cholesterols which were greater than 240.

Was there any data that was collected in those studies which showed that these people actually took 20 milligrams or 30 milligrams, more than what they were supposed to in reference to your question. And were they allowed to do that?

I don't remember how, I mean, if you had a bottle of pills, they could easily take two versus punching out a self-dosing packet.

DR. SEGAL: The answer is that we don't know the answer and the reason we don't know the answer is because there was no diary collected. So we don't really know in these trials how people actually dosed. We just don't know the answer.

CHAIRMAN BRASS: Does sponsor want to comment because I think it was in a blister pack and I think it was --

DR. LAROUCHE: I do have data. It's true that we don't have the daily diary cards which would

tell us whether or not people on an individual day took more than one pill, but what we did have were two things.

One was a survey where we asked people how they dosed and in that survey nearly everybody said that they dosed one pill a day for nearly every day over the whole six months of the primary study. This was a pharmacy study.

And the other thing that we had, which was the objective pill counts, where we showed the percent of the tablets that they actually took, we assumed that they took them if they were missing from the package when the package was returned, divided by the number of days that they had the study drug in hand.

So, if the right number of pills was missing for the number of days they had, that means 100 percent compliance.

So in the 722 people in the pharmacy trial over six months, only 6 percent of people had pills missing that would indicate up to 120 percent compliance, which means that they could have taken as much as one extra tablet every five days. So there really was no evidence whatsoever to suggest that people would be chronically overdosing.

DR. DONALD UDEN: And did the people who

had cholesterols over 240 know it at that time, that the they had a 250 or a 260, when they were dosing? They did didn't they?

DR. LAROUCHE: In the pharmacy study we didn't permit the people on the long-term usage who were outside the eligible range and in study 81, we did permit people on the four weeks of treatment, but we don't have the same assessment available in that.

CHAIRMAN BRASS: Dr. Neill.

DR. NEILL: Primarily to provide comment for FDA staff, nobody has discussed the need in the OTC setting to monitor transaminase levels and whether or not consumers can adequately do that. Sponsor suggested that that's not necessary and I tend to buy that argument at the 10-milligram dose.

The way the package is labeled, if a patient has a cholesterol that drops, they say on that 10-milligram dose, nearly perpetuity, and if it doesn't go down, then they are recommended to see their doctor at which point apparently they'll have appropriate evaluation done, which may or not include transaminase testing.

As this question five, the global question, is structured, I can't help but think that the answer to that is yes, consumers will be able to

use lovastatin safely in the OTC setting given the constraints of what it means to be in an OTC setting and given the way that the label is set up.

I think that's not as much what we're concerned about, but rather when it's not used in what is recommended to be the OTC setting.

CHAIRMAN BRASS: I think the question means in the actual use OTC setting, not as if they follow it as was done in studies. I think this is the question, is actually OTC use, do we have data to say that consumers will in fact use the drug in a way that is safe?

Other questions or other comments? If not, do you want to vote on this one?

Okay, so the vote is on. Assuming that lovastatin 10 milligrams is deemed adequately safe when used for the proposed indication in the target population, has the sponsor presented adequate evidence that consumers will be able to use lovastatin 10 milligrams safely in an OTC setting?

All who feel that the answer to that question is yes, please raise your hand.

DR. TITUS: Seven yeses.

CHAIRMAN BRASS: All who feel the answer to that question is no, please raise your hand.

DR. TITUS: Six noes.

CHAIRMAN BRASS: Any abstentions?

Thank you.

The final question is, assuming that the answer to question three, if you remember what question three was, is yes, i.e., the sponsor has provided sufficient information to support the safety and effectiveness of lovastatin 10 milligrams for the proposed indication in the target population, has the sponsor provided sufficient evidence that lovastatin 10 milligrams can be used safely and effectively in an OTC setting?

It seems to be a combination. So, this seems to be a combination of four and five. So if yes, are any additional studies needed post-approval, what are the key messages that need to be conveyed? I think we've discussed a number of those. If no, what additional studies are necessary to support approval for the OTC marketing?

I might just say that as one of those who voted no on the safety, I would feel much better from a safety perspective if we really had a no holes barred, minimal intervention, actual use profiling of what kind of consumers would actually buy this product, including exposure to what we would consider

high-risk populations.

Not only high risk from a medical perspective, but high risk from misuse because of ethnicity or literacy.

And to understand with very minimal intervention how well consumers can actually self-select, particularly in the perceived risk populations. Again, if somebody with a 250 versus 240 takes it, I don't think anybody is going to feel that societal danger has been done.

Also, I would be very interested, and I don't know how to get this information, but on whether or not how this kind of availability modifies consumer behavior. Is it in fact likely that a consumer will be less likely to see a physician and enroll in intensive care if this is available or isn't it?

I don't know the answer to that and I'm not sure it's an easy question to answer, but I think it's really pivotal in my assessment of what the risk to benefit is.

Because we've talked about a potential benefit in this population that is potentially of some size, a risk that is probably small to exposure per se, but we've all acknowledged that the benefit would be greater if the patients saw a physician and

enrolled in a more aggressive program, even for primary prevention.

And how we offset any movement from this low-gain OTC population away from this bigger-gain prescription population is a very difficult thing for me to assess on a risk to benefit basis with the information we've been provided today.

Are there other comments? Dr. Davidson.

DR. DAVIDSON: My concerns, number one, that self-selection was not to my liking and I don't think it is really a selection that I can feel good about.

And number two, the overall follow-up at 18 months for patients taking the drug was not good either. I didn't see any data on low literacy people, minority people were excluded in some of the studies, and that is not the target population that we're going to address.

And therefore, I don't feel that this drug should be approved for over-the-counter use.

CHAIRMAN BRASS: Yes, Dr. Uden.

DR. DONALD UDEN: To address your point about healthcare providers and not seeking help. I think what we're hearing is that people aren't doing that now.

I think that that is the issue, is that less than the fact that they would be moving away from their practitioners, the fact that they're not going to their practitioners, assuming this OTC population, and that there is a vast unserved population that would have exposure to this that isn't getting that exposure by not seeing a physician.

CHAIRMAN BRASS: Yes.

DR. MOLITCH: I'd like to add to that in an editorial fashion. If patients are not seeing their physicians, I'd much rather see much greater efforts expended by drug companies and healthcare providers in getting the patients with higher cholesterols, with higher risks, into get to these healthcare providers than for the lot of expenditure that is going to be put forward on this particular aspect for a very low-risk population where a lot of money is going to be spent for a very low decrease in overall events.

Where that same money could be spent in a high-risk population for a much better cost ratio.

CHAIRMAN BRASS: Other comments? Are there other issues that the agency would like additional input on or expansion of the discussion on?

DR. KATZ: We actually would like a vote

to that question.

CHAIRMAN BRASS: I'm sorry. Okay. It's kind of complicated, because of the way we handled three, but let's give it a try as they say.

Let me try put it this way. Let's vote on the following question. Has the sponsor provided sufficient evidence that lovastatin 10 milligrams can be used safely and effectively in an OTC setting? Let's just leave it at that.

All who feel that the answer to that question -- I'm sorry, yes, please.

DR. EDWARD KRENZELOK: I'm sorry. I need a clarification because we broke effectiveness down into decreased LDL or evidence-based outcome, so are we going to vote based on decreased LDL or on the evidence-based improvement and outcome?

CHAIRMAN BRASS: What I would propose is dealer's choice. And I will, to give a sense of the agency of where we're coming down on effectiveness, they know we don't think it's been proven that it decreases cardiovascular events, so let's just avoid -- I'm happy to do it twice, but I propose we do it once with the wording as I read it. Is that acceptable to the Committee?

DR. ORLOFF: And to the FDA as well.

That's fine.

CHAIRMAN BRASS: Okay. Yes, Dr. Neill.

DR. NEILL: Just in advance of making the vote, a couple of comments have been made about the potential public health benefit that would accrue by virtue of the vast at-risk population in this low-risk group that is going to benefit from this.

And comments have also been made that the NCEP guidelines do not current recommend drug treatment for this group. And I don't think any of us should lose site of the fact that a change in those guidelines could probably equally effectively result in a public health benefit through the prescription route without OTC consideration at all, as much as our decision to step in front of NCEP if you will, or to urge the adoption of that kind of guideline.

And so, in trying to consider in my own mind whether or not how to think about the potential public health benefits of this and whether or not we would be doing a public health disservice by not making this OTC. There are other avenues to address that.

Lastly, there is an issue which hasn't come up as much today and probably doesn't pertain as much to this specific vote, but I feel like it's got

to get out at some point which has to do with the fact that this medication in not very similar form, but this medicine already exists over the counter and I feel torn, as I'm sure the sponsor does, by the realization that FDA is being asked to regulate lovastatin as a drug while it's already available over the market in a form that is not able to be regulated by the FDA for a variety of reasons.

And I'm not privy to all of the court issues that have gone on related to the regulation of that, but there is a clear paradox when the FDA is being asked to regulate lovastatin in an OTC fashion, and we've spent a lot of time on this today, and on the other hand, it already exists in a fashion which the FDA can't touch.

At some level, obviously not here today or by this group or FDA, but probably downtown, that will need to be addressed. And regardless of how this vote comes down, it won't change the fact that it's available.

CHAIRMAN BRASS: I think the points you raised are extremely important; however, I think we have to be a little bit careful about how we extrapolate certain information.

Somebody earlier said two wrongs don't

make a right and just because it's done wrong once doesn't mean it should be wrong again.

Additionally, I'm not at all convinced that a consumer who is quite comfortable taking an herbal product for control of their cholesterol would have any interest in an OTC product.

When my patients with that kind of cultural bias, they have a blanket aversion to drugs, period. And herbs and dietary supplements are a completely different thing. And OTC drugs would be just as abhorrent to them as going to a doctor and getting drugs.

So I think our identification of all the deficiencies in our existing societal ability to treat high cholesterols has to be extrapolated very cautiously to how the massive availability would or wouldn't impact that problem and at what risk.

Are there other comments? Dr. Clark.

DR. CLARK: Yes. I just wanted to refer back to the public comments this morning. All the comments were in favor except one, but the reasons for those comments had to do with the issues of increasing access, issues related to patient and public becoming more interested in self-help and participating in their own healthcare, and issues of looking for better

strategies for cholesterol lowering in individuals and populations.

And it just doesn't seem that those have been issues that were important to any of these deliberations here and I was just wondering if the people who presented were kind of off base in terms of what they were responding to.

Because those are important issues, but they really haven't been a part of any of the discussions here, and I'm not saying that's not correct, but I would hope some response to those.

CHAIRMAN BRASS: I think your point is correct, but I will point out that no data has been presented to us to allow us to make those relative judgements. And those go to some of the points your hearing now about how availability, who would actually use it, and at what potential benefit. Dr. Gilliam.

DR. GILLIAM: I was going to echo that point somewhat in that although -- the point I was going to make is that although there are going to be people who are going to have cholesterols out of the range and who probably shouldn't be taking this product. But I guess I would rather see them take something if they're not going to come in and see whoever their healthcare provider is.

So I guess that's the main comment I want to make there.

CHAIRMAN BRASS: And again, I think there is broad agreement with that if we could assess what the relative benefit of that versus a relative risk of that will be. And that's where the absence of specific adequate information in several areas has been raised today, that makes that a challenging conclusion for the Committee to draw. Dr. Johnson.

DR. JULIE JOHNSON: I have a question to clarify what the question is going to be.

CHAIRMAN BRASS: I knew we should have voted already.

(laughter)

DR. JULIE JOHNSON: Are we going to be voting on something like if additional data are provided is the product someday approvable?

CHAIRMAN BRASS: No. It's on the information that has been presented to us today and we've made suggestions as to already what type of data would help us resolve some of the residual conclusion. That's my interpretation. Does the agency agree?

DR. SLATER: The sponsor would not agree. Excuse me doctor.

CHAIRMAN BRASS: I'm sorry.

DR. SLATER: I really truly would not know how we could go about to gather the kind of information you want to know.

Seriously, in the absence of actually a post-marketing study where that 1-800 number for example was used to collect the information, whether the person did indeed get their cholesterol, whether it was in range, out of range, whether they did call their doctor or not.

In order to try and conceptualize the kind of vast body of information that you folks are asking for, is just not practical and doable.

CHAIRMAN BRASS: That's not the question before the Committee now.

DR. SLATER: It's the same answer as you are going to vote with or without suggestions. We desperately need suggestions or we're going to say this is just not a doable program, and that's really what we're asking of you right now.

The only way we could get some of this longer term information, demographic information, etc., is through the actual marketed product. We can't do a study.

CHAIRMAN BRASS: Well, I want to emphasize that the Committee is advisory to the FDA, not to

sponsor and I think that we have heard a number of suggestions that perhaps at a later --

DR. SLATER: You said there were suggestions and I'm saying I do not have those suggestions that I can translate into something practical.

CHAIRMAN BRASS: Dr. Katz.

DR. KATZ: To answer your question as to how do we want you to answer the question, the first part of the question is really yes or no question.

If you answer yes, then you would go on to part A. If you answer no, then you go on to part B which would then give us some additional information.

DR. JULIE JOHNSON: Well, I guess my confusion is that we essentially answered, or the Committee answered no to question three in that we answered no to the first part of question one, which the way this is written, we wouldn't even answer question six because we didn't answer question three as yes. So that's where I'm confused.

DR. KATZ: Well, basically again, since you actually really didn't answer question three, you answered question one in two parts, and I want to make sure for the record on question six that we really do have your answer with regard to approvability. So

that's the distinction that I'm trying to make.

CHAIRMAN BRASS: Okay. So the answer to your question is based on the currently available data that has been presented to us. Has the sponsor provided sufficient evidence that lovastatin 10 milligrams can be used safely and effectively in an OTC setting?

All who feel the answer to that question is yes, please raise your hand.

DR. TITUS: One yes.

CHAIRMAN BRASS: All those who feel the answer to that question is no, please raise your hand.

DR. TITUS: Eleven noes.

CHAIRMAN BRASS: Abstentions? One yes, eleven noes, one abstention.

Therefore, if no, what additional studies are necessary to support approval for OTC marketing? And I think several suggestions were made on both the safety and on the efficacy side.

And let me just emphasize that on the efficacy side, the suggestions were made in terms of better defining and using LDL as a surrogate in comparing to prescription use was one suggestion that was made.

Are there other suggestions that have not

previously been discussed that people would like to put on the table?

DR. DAVIDSON: I go back to my basics. Number one, the lipid collection. Number two, a compare with even lovastatin, but used in the manner that we use it today and do the studies inclusive and not exclusive.

DR. GELATO: I think it goes back to what Dr. Clark was saying in that people who addressed us this morning from the community were making a big push for making this drug available to people who didn't have access. And I'm not sure I really understand who those people are.

It would help me to know what we're talking about and who we're trying to target this for, because when I look at the demographics that were presented by the sponsor, those people that you showed who were taking this drug were people who clearly had access.

They had health insurance, they were fairly well educated, and had fairly good salaries for the majority of people.

So I think it is important to deal with Dr. Clark's issue about who are the people who don't have access and who are we trying to target here,

because that's what the other groups were making a compelling case for, and I think it is a compelling case, but it wasn't really answered in my mind as to how that was actually going to be addressed.

CHAIRMAN BRASS: Dr. Davidson.

DR. DAVIDSON: The two groups that were here this morning represent minorities. ABC represented the African-American community and ICPS represents the Latino in this community. And obviously looking at what happened today, they were not represented in the clinical trials.

And access to care, education for these groups is clearly a necessity. And unless we partner with the pharmaceutical companies, with the industry, we're not going to get these people treated.

And I want to tell you, there are more than 60 million minorities in just those two communities living in this country. That's a big market for the industry, but we need to see some efforts directed to those communities in clinical trials and in events that we can reduce in those communities.

CHAIRMAN BRASS: Yes, sir.

DR. JENKINS: Yes, Dr. Brass. I'd like to follow up.

Clearly this is a very difficult issue and I think you heard Dr. Slater pleading for advice on how they could do the studies that would make the Committee feel comfortable to recommend approval of this product at this dose OTC.

I think it was you earlier that recommended something that you referred to as a no holes barred, actual use, real world study, and I'm wondering if you can provide the sponsor and us with some more details of what that study would look like.

How would you do it? What endpoints are you talking about looking at in that study? And maybe we can use that information.

CHAIRMAN BRASS: Can I stop using my government consulting rate and start using my other consulting rate?

I think the issues are important here, had having sat on this Committee for about forever, that every time an open-label comprehension study is presented, the issues are exactly the same.

The ability of a consumer, usually biased towards high income, high literacy, Caucasian, to with the label in front of them, read it, and check the boxes on a multiple choice question.

And I do not feel personally that that

reflects how consumers actually buy these products. And I think that you need a minimal cueing study so that you're not biasing towards what the responses, or even the indicational risks are, what the study objectives are.

That you need to be able to have a sufficiently broad population that is, if anything, enriched in the risk groups, and as I said before, the risk groups are broadly defined based on literacy as well as medical problems. And challenge the hypothesis that they will use it correctly, not do a study biased to get the consistent with result.

And I think that in any other type of scientific trial design, this kind of limited challenging of hypothesis to conclude the hypothesis is true, would not be tolerable.

DR. GILLIAM: Now that we've voted, I'm confused. Because it seems to me that if you read these questions, most of us voted yes on question five, or it was six to five or whatever.

If you voted yes on that question, then it logically seems to me that you would have to vote yes on question number six, because it goes to consumers that the sponsor has been able to say that consumers will be able to use it in over-the-counter setting,

and then question number six says evidence that it can be used safely and effectively. And it seems like they are really the same question to me.

CHAIRMAN BRASS: Well, the issue was on the effectiveness question, people did not vote yes. So for safe and effective, the end statement captured the either yes vote. Yes.

DR. TAMBORLANE: To get back to your question about how you design a study. I would suggest you could survey large groups of people and find out whether they are interested in lipid-lowering agents, what have been the obstacles to be involved with using those drugs, are those people who felt that they had an obstacle because they had inadequate medical care? Those people could be given the drug and asked to read it and see if they follow through.

I think there are ways to start with a fairly hands-off way to try to direct people that way.

CHAIRMAN BRASS: Because even the type of assessments for example, I think the issues about whether patients are motivated to decrease their fat in their diet and all those other types of things. I've never had a patient come to my office who didn't claim they were on a fat-free diet. That's just what patients say. Dr. Temple.

DR. ROBERT TEMPLE: Well, I'm certainly on a fat-free diet, except for those cookies. That was just a small break.

There are really two sets of questions that keep coming around and around. One is how sure are we that the identified population would actually benefit, and the other is, if they could, could they use this drug properly in an over-the-counter setting.

Do you all have any sympathy for the idea that the choice of dose is a problem? That is, using 10 milligrams when all your data is at 20? And that focusing much more on an identified group with an explicitly low HDL would be sort of a preliminary basis for starting to do the studies to see whether it could be used OTC?

Because at least then you might say, okay I've got the TexCAPS population or something like it.

CHAIRMAN BRASS: Dr. Johnson.

DR. JULIE JOHNSON: Well, I sort of thought about that and you can probably make two arguments and you can make one argument that it's already been documented in a large randomized placebo-controlled trial that those people, the AFCAPS population, should be treated and they should be treated with 20 to 40 milligrams to a goal of less

than 110. So how do you ethically do that?

As the discussion went on today I was sort of struggling on today with should we recommend that their label include an HDL criterion, but then if you do that, you're really capturing the AFCAPS population and you're treating them less effectively than the AFCAPS study. So that's I think the difficult part.

DR. ROBERT TEMPLE: Well, the second part is in some ways the question. There are people who come before you and say, well yes, maybe the compliance won't be as good as if someone's actually with his or her physician, but I'll treat so many more people for some slightly mysterious reason that I'll end up getting more of those people treated than I otherwise would, and that might be an added benefit.

I guess what strikes me then is that at least you're talking about OTCness again and you're not arguing about whether you have any effectiveness of the regimen, you're arguing about whether it can be give in an OTC environment, which is at least conceivably studiable.

Whereas for reasons the company gave, they can't study the less ill populations because they'd have to study 200,000 people, which is another way of saying the benefit is very small, of course.

CHAIRMAN BRASS: But obviously a positively controlled study like that can be done ethically in that kind of situation, but the design would be -- I would submit if you compare 10 milligrams over the counter to that, you already know the answer is negative, because 20 milligrams didn't work. Half the patients needed to be titrated to 40.

So that if you know that 20 milligrams doesn't work at a fixed dose to achieve the same efficacy, then you're really trying to replicate the titration in the OTC setting as well.

DR. ROBERT TEMPLE: Well, actually focus it on a population that has a poorer HDL, because there you have the data and it's going to be very hard to get the data in the very high HDL population, for the reasons that everyone has been given.

But it seems to me the implication of that hasn't been accepted, which is that the benefit is extremely small, probably not demonstrable in any real-world study, which makes one ask whether that's a really good thing to do.

But in the AFCAPS population, there is some evidence that it is a good thing to do, otherwise we wouldn't have approved it for the Rx labeling.

So the question then could become can you

deliver that treatment in an OTC setting? I don't think I know what the answer is, but at least that seems like a reasonable question.

DR. ORLOFF: I think just to expand a little bit, frankly, one of the questions that we never really did get to in a broader sense today was the viability of hypercholesterolemia generally as an OTC disease. In the past we had stated that it wasn't.

To expand on Dr. Temple's proposition, we've talked today about limited indication for use in a limited dose. What about the possibility? How do people feel about the expansion of the indication and the expansion of dose?

We have a lot of indications for the use of cholesterol-lowering drugs that are contained in the prescription labeling.

Again, to harken back to what Dr. Temple just said, can that, can those benefits, be accrued with an acceptable level of risk in an OTC setting?

DR. GANLEY: I just want to follow up on that because I think one of the differences in the paradigm of treatment has been I think of a set dose rather than a titrated dose. And I guess my question is, is 40 milligrams or even 80 milligrams, an

acceptable dose as an OTC dose and if it is not, why is it not?

You've already voted on 10 milligrams as a safe dose. We've heard information from the sponsor that liver disease is very rare. Rhabdomyolysis is likewise rare. And even if you give a drug that inhibits the metabolism, it's still rare. So why isn't 40 milligrams or 80 milligrams?

And it also brings into play the issue that was brought out somewhat today and also in the Part 15 hearing we had whereby it's not just this population that may need treatment, it's the population that clearly would benefit here that needs treatment. Is that an OTC population?

And could you come up with a paradigm where there is a titration in an OTC setting where you could carry it to 40 milligrams or 80 milligrams? And if the drug is so safe, why not just start at 40 milligrams?

CHAIRMAN BRASS: Dr. Clark.

DR. CLARK: This being my first attendance at one of these meetings, I feel I can ask this question.

As Dr. Orloff pointed out this morning, this is the third time I guess this question has come

before this Committee in the last five years, and I'm curious as to whether or not there is movement in some direction or if these are just different issues each time as it relates to cholesterol lowering in OTC?

CHAIRMAN BRASS: I think we are about to start on another meeting right here.

(laughter)

But I think the questions you've raised are important, but if I could extrapolate from what's been discussed any my own opinions will obviously contaminate this, I think you're hearing some things about where the bar would need to be placed in order to convince the Committee about that. And that bar would be no different for 40 or 80 versus 10.

In fact, the ability to convince the Committee of cardiovascular endpoints at different doses and at different populations would probably be a lot easier.

The ability to convince the Committee that the OTC population would use it the same way, to replicate that efficacy, as has been seen in the prescription setting, I think would still be there, and many of those concerns would be there. And the need to define the safety in a real OTC use would still be there.

So I think the themes are recapitulated and what you've done and your hypothesis would be to make it easier to extrapolate the benefit and more challenging to show that the OTC population replicated that benefit in safety. I don't know what other members -- Dr. Johnson.

DR. JULIE JOHNSON: Since you're asking sort of broad generic questions, I think this came up multiple times at the Part 15 hearing. I mean, this is also very possibly a category that fits very well in this proposed third category of drugs which are dispensable by a pharmacist, but kept behind the counter and monitoring could be done with these little things that they have sitting on their counter. And obviously that is not in our purview and maybe not in the FDA's. I don't know if that's a legislative thing or not.

But that's another potential, especially if you were going to be considering higher doses or methods that require dose titration that I'm not convinced patients could undertake.

DR. DAVIDSON: My concern is cardiovascular disease in the United States remains a very important issue. It's expensive. It's increasing or at least it is not declining.

And my concern is if we allow uninformed people to take a drug believing that that drug is a miracle drug that is going to prevent events in the future, knowing that no drug, no statin, will prevent 100 percent of the MIs, I think we are going to be giving a message that is not a clear message to the community.

It has been stated clearly. There are some things we need to do. We need to do education to the whole country. Nutrition remains a very important arm of this part. Exercise remains a very important arm of this part. Maybe aspirin use is as important as in the statins. Because if a statin will lower the MIs by 90 percent, then I think that over the counter with the safety that they have is good.

But the consumer, and I may be wrong, may not be ready to tell them, that this is a drug, nobody is going to follow up with lipids, nobody is going to follow up with any side effects. You also showed that the higher the dose, the more side effects we have.

Then I think we need to be very careful when you ask me if we go to a higher dose, is that really an over-the-counter medication and your first question is, is actually dyslipidemia an over-the-counter treatment. It's not just cholesterol, it's

triglycerides, it's LDL, it's total cholesterol, and how high is the LDL, and the whole thing.

It is a lot more difficult to assess the lipid profile of a patient than just looking at LDL.

CHAIRMAN BRASS: Yes.

DR. MOLITCH: In addressing the issue of dose titration by patients themselves going up to 40 or 80 milligrams per day. For those of us who actually see patients and prescribe these drugs in practice, every time you try to measure something and then get them to increase the dose because their LDL is not below 100, the patients resist doing it.

They complain, they think, well my condition is worsening, I have to take more drug, and so either they don't do it sometimes or if they'll do you have to spend 10 or 15 minutes visiting the patients why they need to do so.

And it's actually very difficult to titrated doses upwards, even when there is a very clear rationale, whether it's for cholesterol or blood pressure medications or oral hypoglycemic agents for diabetes control. Every time you increase the dose the patients get worried and there is a resistance that sets in.

So, it would behoove you I think to really

be able to show that patients can self-titrate themselves upwards without a physicians assistance when it's already difficult to do even with a physician's assistance.

DR. GANLEY: I think in response to that, we already have drugs were people self-titrate. Granted they are based on symptoms. For example, we have ibuprofen products where they will take one or two tablets.

And I think that my interest is that we should try to maximize benefit here and one way to do that is to have a goal for people. It's easier with symptoms because you know what the goal is. It's a little more difficult here, but maybe not impossible to achieve.

So I think it becomes an important question. And if a consumer's fears are unrealistic in your view, then there is a message that possibly could get out if you had an OTC product that started at 40 milligrams and went to 80 milligrams. Using some paradigm that was understandable.

And I think it really comes down to what was mentioned previously about what the absolute benefit is and what is the risk of a higher dose. So that becomes very important in looking at that

question.

DR. GRADY: Just to follow up on that. I think what bothered me most about this whole regimen was that the dose had been taken so low and the population chosen is so low risk, that then you have to begin to wonder if there is really going to be any benefit. And if there is not much absolute benefit, then any absolute risk will outweigh that.

So I actually like the idea of thinking about over-the-counter use of somewhat higher doses, particularly if it could be monitored using a protocol by nonphysician personnel. Because it is just a protocol and it doesn't really require a physician to do this.

In fact, I think probably nonphysicians could do it better if there was some requirement for periodic monitoring.

DR. DAVIDSON: The problem is that over the counter does not allow you to have a protocol.

CHAIRMAN BRASS: Anything else from anybody? In case anybody missed anything, we are going to do this all again tomorrow.

(laughter)

Let me close by thanking very much the sponsor -- or wait a second, wind it out.

DR. TITUS: I'd appreciate before you all leave to turn in these red books to me or Kathleen and if you talk to Kathleen or myself, we have some dinner options available.

CHAIRMAN BRASS: Let me thank the sponsor and their representatives, the agency and their representatives, and all the Committee members for their excellent input. I apologize we ran 28 minutes late, but it was all those extra questions you threw in.

We are now adjourned.

(Whereupon, the foregoing matter concluded at 5:29 p.m.)

C E R T I F I C A T E

This is to certify that the foregoing transcript in the matter of: JOINT MEETING OF THE NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND THE ENDOCRINOLOGIC AND METABOLIC ADVISORY COMMITTEE

Before: FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: THURSDAY, JULY 13, 2000

Place: BETHESDA, MARYLAND

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.

Rebecca Davis

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