U.S. FOOD AND DRUG ADMINISTRATION

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NONPRESCRIPTION DRUGS ADVISORY COMMITTEE (NDAC)
WITH THE
GASTROINTESTINAL DRUGS ADVISORY COMMITTEE (EDAC)

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JOINT PUBLIC MEETING

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FRIDAY,
JUNE 21, 2002

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BETHESDA, MARYLAND

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The Joint Meeting commenced at 8:00 a.m. in the Versailles Rooms I and II at the Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, Louis R. Cantilena, Jr., M.D., Chairman, NDAC, presiding.

MEMBERS PRESENT:

Nonprescription Drugs Advisory Committee:

Leslie Clapp, M.D., Member
Frank F. Davidoff, M.D., Member
Julie A. Johnson, Pharm. D., Member
Y.W. Francis Lam, Pharm. D., Member
Sonia Patten, Ph.D., Consumer Rep.
Donald L. Uden, Pharm. D. Member
Henry W. Williams, Jr., M.D., Member

Gastrointestinal Drugs Advisory Committee:

M. Michael Wolfe, M.D., Chair
Michael Camilleri, M.D., Member
Susan Cohen, Consumer Representative
Byron Cryer, M.D., Member
Ronald P. Fogel, M.D., Member
Nancy L. Geller, Ph.D., Member
George S. Goldstein, M.D., Guest Industry Rep.
John T. LaMont, M.D., Member
Robert A. Levine, M.D., Member

NDAD Consultants Present:

Eric P. Brass, M.D., Ph.D.
Edwin E. Gilliam, Ph.D.
Richard A. Neill, M.D.

NDAD Industry Guest Present:

Michael C. Alfano, D.M.D., Ph.D.

FDA Staff Members Present:

Jonca Bull
Charles Ganley, M.D.
Florence Houn
Victor Raczkowski, M.D.
Sandra Titus, Ph.D.

Also Present:

John A. Gans, Pharm.D., American Pharmaceutical Association
Linda Golodner, National Consumers League
Robert M. Niecestro, Adrix Labs
Susan Winckler, American Pharmaceutical Association

A-G-E-N-D-A

P-R-O-C-E-E-D-I-N-G-S

(8:06 a.m.)

DR. CANTILENA: Good morning everyone and welcome to the Nonprescription Drug Advisory and the GI Drug Advisory Committee. I'm Dr. Lou Cantilena, Chief of Clinical Pharmacology at the Uniform Inservices University here in Bethesda. I'll be chairing this meeting.

We will start off with the conflict of interest statement. Actually we'll start off by going around and introducing ourselves. I have already done that so if we can start at this end over here and introduce this way.

DR. GOLDSTEIN: I'm George Goldstein. I'm the industry representative for the Advisory Committee.

DR. ALFANO: I'm Michael Alfano, Dean of Dental School at NYU and the ILR at the OTC.

DR. JOHNSON: My name is Julie Johnson. I'm from the University of Florida and I'm a member of the Nonprescription Drug Committee.

DR. CRYER: Byron Cryer, member of the Gastrointestinal Drugs Advisory Committee. I'm a gastroenterologist from the University of Texas Southwestern Medical School, Dallas.

DR. BROWN: I'm Eric Brown from Harvard UCLA Medical Center, Department of Medicine. I'm a

consultant to the committee.

DR. CAMILLERI: I'm Mike Camilleri, gastroenterologist from the Mayo Clinic, Rochester. I'm a member of the Gastrointestinal Drugs Advisory Committee.

DR. FOGEL: I'm Ron Fogel, Division Head of Gastroenterology, Henry Ford Health System, and I'm a member of the GI Drug Advisory Committee

DR. WILLIAMS: I'm Henry Williams from Howard University and a member of NDAC.

DR. UDEN: I'm Don Uden from the University of Minnesota College and member of NDAC.

DR. GELLER: I'm Nancy Geller. I'm the Director of the Office of Vital Statistics Research at the National Heart, Lung, and Blood Institute and I'm a member of the GI Advisory Committee.

DR. CLAPP: I'm Leslie Clapp, pediatrician, Buffalo, New York, Associate Professor of Pediatrics at SUNY UB. Also a member of NDAC.

DR. TITUS: I'm Sandy Titus. I'm the Executive Secretary to NDAC.

DR. NEILL: I'm Richard Neill. I'm a family physician and consultant to NDAC.

MS. COHEN: (Inaudible).

DR. GILLIAM: I'm Eddie Gilliam. I'm a

family nurse practitioner from Tucson, Arizona and a member of NDAC.

DR. LEVINE: I'm Bob Levine from State University of New York, Upstate Medical University in Syracuse. I'm a gastroenterologist and member of the GI Advisory Board.

DR. LAM: I'm Francis Lam. I'm a member of the NDAC committee. I'm from the University of Texas in San Antonio.

DR. PATTEN: I'm Sonia Patten. I'm an anthropologist on the faculty at McAllister College. I'm from Minneapolis, Minnesota, and I'm a consumer representative on NDAC.

DR. LaMONT: I'm Tom LaMont. I'm a gastroenterologist, Chief of the Division of Gastroenterology at the Medical Center in Boston and a faculty member at Harvard Medical School.

DR. DAVIDOFF: I'm Frank Davidoff. I'm an internist and former editor of the Anals of Internal Medicine and I'm a member of NDAC.

DR. KATZ: I'm Linda Katz, Deputy Director of the Division of Over-the-Counter Drug Products of the FDA.

DR. GANLEY: I'm Charlie Ganley, Director of Division of Over-the-Counter Drugs at FDA.

MS. BULL: Good morning. Jonca Bull, Office Director, Office of Drug Evaluation and Center for Drug Evaluation Research.

DR. RACZKOWSKI: Good morning. I'm Victor Raczkowski. I'm the Acting Director of the Division of Gastrointestinal and Coagulation Drug Products.

DR. HOUN: I'm Florence Houn, Director of Office of Drug Evaluation Three and FDA.

DR. CANTILENA: Thank you. Now Dr. Titus will go through the conflict of interest statement for the June 21st Meeting of Nonprescription Drugs and Gastrointestinal Drugs Advisory Committees

DR. TITUS: The following announcement addresses conflict of interest issues associated with this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

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

Ft. Michael Wolfe is excluded from

participating in today's discussion and vote concerning Prilosec 1.

Dr. Eric Brass has been granted a waiver under 18 U.S.C. 208(b)(3) for unrelated consulting with competitors. He receives less than $10,000 a year from two of the firms and between $10,001 and $50,000 per year from the third firm.

Dr. Michael Camilleri has been grated a waiver under 18 U.S.C. 208(b)(3) for his participation as a consultant on unrelated matters for five firms that have financial interests in competing products. He receives less than $10,001 a year from each firm.

Susan Cohen has been grated waivers under 18 U.S.C. 208(b)(3) and 21 U.S.C. 355(n)(4) amendment of Section 505 of the Food an Drug Administration Modernization Act, for ownership of stock in competitors. The first two stocks in competitors are valued between $5,001 and $25,000. The other two stock holdings are valued between $25,001 and $50,000.

Dr. Byron Cryer has been granted waivers under 18 U.S.C. 208(b)(3) and 21 U.S.C. 355(n)(4) amendment of Section 505 of the Food and Drug Administration Modernization Act, for shares of stock in the manufacturer of the product at issue and a competitor; and for consulting on unrelated matters

for a competitor.

The stock in the manufacturer of the product at issue and a competitor is valued at less than $5,001. The unrelated consulting for a competitor is valued between $10,001 to $50,000.

Dr. Ronald Fogel has been granted a waiver under 18 U.S.C. 208(b)(3) and 21 U.S.C. 355(n)(4) amendment of Section 505 of the Food and Drug Administration Modernization Act, for shares in a sector mutual fund valued between $5,001 and $25,000.

Dr. Robert Levine has been granted waivers under 18 U.S.C. 208(b)(3) and 21 U.S.C. 355(n)(4) amendment of Section 505 of the Food and Drug Administration Modernization Act, for shares of stock in a competitor valued between $25,001 and $50,000.

A copy of these waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would like to note for the record that Michael Alfano, Ph.D., and George Goldstein, M.D., are participating in this meeting as industry representatives, acting on behalf of regulated industry. As such, these participants have not been screened for any conflicts of interest.

In the event that the discussions involve any other products of 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 products they may wish to comment upon.

DR. CANTILENA: Thank you, Dr. Titus.

We will now hear from Dr. Raczkowski from the FDA to open up the issues for discussion.

DR. RACZKOWSKI: Good morning. My name is Dr. Victor Raczkowski and I'm the Acting Director of the Division of Gastrointestinal and Coagulation Drug Products. On behalf of FDA I would like to welcome members of the Nonprescription Drugs Advisory Committee, the Gastrointestinal Drugs Advisory Committee, as well as members of the public

I would like to briefly set the stage for today's deliberations for the Joint Advisory Committee Meeting. This is the second time that this joint committee is meeting to discuss whether the data are sufficient to recommend approval for Prilosec 1, or

omeprozole magnesium, for use in the over-the-counter setting.

The first time this joint committee met on this issue was October 20, 2000. At this time different over-the-counter uses are being sought by the sponsor, Procter and Gamble and AstraZeneca.

Today the new use that will be considered by the Joint Advisory Committee is for the prevention of the symptoms of frequent heartburn for 24 hours. This proposed use indicates that Prilosec 1 is only for those who suffer heart burn two or more days a week.

The directions for use proposed by the sponsor is that consumers swallow one tablet which is equivalent to 20 milligrams of omeprozole with a glass of water every morning and to take one tablet every day for 14 days.

This new use and a new direction proposed for Prilosec 1 by the company reflect the underlying properties of Prilosec 1. Unlike the histamine H_2-receptor antagonists or antacids which can be used to treat heartburn, for example, the ability of Prilosec 1 to inhibit gastric acid secretion has a delay in onset and requires several days of continued treatment to build up to its maximum effect.

In other words, this new use proposed by Procter and Gamble and AstraZeneca means that the drug is not to be used to treat acute symptoms of heartburn or to prevent meal induced heartburn. Rather, it is to prevent frequent heartburn.

Moreover, these directions mean that consumers should not take Prilosec 1 episodically missing doses or skipping doses. Rather, consumers should take Prilosec 1 daily for 14 days.

In support of these new uses, the sponsor has conducted new labeling comprehension studies and has conducted new actual use studies and we'll be hearing more about these later this morning.

In contrast, the sponsor has not provided additional efficacy, safety, or pharmacokinetic or pharmacodynamic data. Rather, the studies on efficacy, for example, that were used in the previous submission are being used to support this newly proposed use.

Today we have many issues we are asking the Advisory Committee to consider. One issue is that one of the cardinal manifestations of gastro esophageal reflux disease, or GERD, is frequent heartburn and, as I've indicated, the sponsor is taking a new use for the prevention of frequent

heartburn in the over-the-counter setting.

One may believe, for example, and this is open for discussion by the Advisory Committee members, that this disease, GERD, requires diagnosis and monitoring and management by a healthcare professional such as a physician. If so, then consumers with this disease of GERD have to make a choice about whether to see a physician or whether to self-administer Prilosec 1. We will be seeking the Advisory Committee's advice on whether this is an issue or not.

Additional issues that will be discussed by the Advisory Committee are whether consumers can appropriately self-select to use Prilosec 1. A third is whether or not consumers use the drug appropriately. The fourth issue is whether 14 days is an appropriate treatment duration. Finally, we will be asking the committee about its recommendations for approvability of Prilosec 1.

We have a full agenda today and we look forward to your deliberations. Thank you very much.

DR. CANTILENA: Thank you very much for those comments.

We will now move into the open public hearing. For the open public hearing we have four speakers. I would like to remind the speakers that

prior to starting, if they have any conflicts of interest those should be stated for the committee.

Also, each speaker has five minutes for his or her talk. The first speaker, Linda Golodner from the National Consumer's League in Washington.

Linda.

MS. GOLODNER: Thank you. My name is Linda Golodner. I'm President of the National Consumers League. America's oldest consumer advocacy organization is pleased to testify today before the committees on the possible switch of Prilosec to nonprescription status.

NCL has a long history of providing information and educational materials to consumers so they can safely and effectively use medications, both prescription and nonprescription.

I would like to inform the committee that occasionally the League receives financial support from pharmaceutical companies for specific consumer education projects in which we maintain full editorial control.

In addition pharmaceutical companies have supported our annual dinner and conferences. These contributions amount to less than one half of 1 percent of our annual operating budget.

I personally do not have stock in or consult with any pharmaceutical companies. The National Consumer League did not receive any financial incentive to appear at this meeting.

Many of the 60 million Americans who suffer from heartburn are not satisfied with current OTC medications available. Making Prilosec, a proton pump inhibitor, available without a prescription would provide more options when self-treating heartburn symptoms. Heartburn is one of those conditions that when you have it, you know you have it. Therefore, we feel that consumers can adequately self-diagnose this condition.

If this medication were available OTC, consumers would be able to effectively prevent frequent heartburn with Prilosec without having the trouble of going to the doctor or having the expense of going to a physician.

Consumers today are taking a more active role in their healthcare including self-diagnosing and self-medicating. NCL is working to help consumers understand what medications they are taking, why they are taking them, and how to take them effectively.

Because of this trend in self-medication any medication slips from prescription to

nonprescription status must first be found to be safe by the FDA by this committee and reported to the FDA and, if allowed on the market, there should be clear understandable information available at point of sale and through advertising for consumers to use that product appropriately and safely.

In order to better understand what consumers know about OTC medications and how they are using them, the National Consumers League commissioned a survey on consumer's use and attitudes regarding OTCs.

According to survey, consumers generally have a favorable impression of OTC drugs and use them regularly to treat minor health conditions. But one-third of consumers do not **regularly** read the labels of OTC products before purchasing or using them. That includes all OTC products that they are taking.

One-quarter of those surveyed had some trouble reading and understanding the label. Another one-third of the consumers reported taking more than the recommended dose some or most of the time, while more than one in five consumers take OTC medicines for longer than recommended.

These survey results underscore the need to use clear, good-size type on the labels and that

specific directions for dose and how long to take the medicine be emphasized on the package, on the label, and in any promotional material.

A recent survey by NCPIE, a patient education advocacy group of which NCL is on the board, also found that consumers need to be better informed about using OTC medications appropriately. The survey found that 95 percent of the consumers read some portion of the label but they do so selectively.

When buying an OTC product the first time only a third look at the active ingredient and one in five seek out warning information. Over a third of the consumers combine nonprescription medications when they have multiple symptoms.

On a positive note the survey also found the majority of consumers get their information about OTC medications from their health professionals, and that the health professionals were very willing to discuss OTC medication use with their patients.

What is clear from these surveys is that consumers need to be better informed when using OTC products, but also that the involvement of health practitioners could increase consumer understanding of OTC use. Therefore, I would hope that there would be efforts by the manufacture to encourage healthcare

professionals to educate consumers in the use of an OTC Prilosec.

If the FDA determines that Prilosec, in 20 milligram doses for 14 days, can be taken safely by consumers with a prescription, we recommend that there be appropriate labeling on the medication to ensure proper use by consumers, including clear information about who should not be taking the medication, especially those who take drugs that would interact with Prilosec.

There must be clear label directions on how to take it, specific listing of warning symptoms of when consumer should go to the doctor. NCL wants to ensure that consumers seek medical attention if the recommended Prilosec regimen does not relieve their heartburn or if they experience certain symptoms.

Clear label warnings and information should help prevent consumers from delaying seeking necessary medical attention. Of course, the label should also list possible side effects and encourage consumers to continue to have regular physician visits while taking Prilosec. Consumer should also be instructed to inform their physician that they are taking Prilosec, and to contact their physician or pharmacist if they have any questions about the

medication.

NCL recognizes that pharmaceuticals are an important component in assuring good health, however, whether by prescription or over-the-counter they must be taken seriously. Just because a drug is available on the shelf of a grocery store or discount store does not make it more safe than if a doctor prescribed this drug.

Physicians, nurses, physicians assistants, pharmacists, and other healthcare professionals play a vital role in ensuring that consumers use their medications effectively. Thank you.

DR. CANTILENA: Thank you very much. Our next speaker is Dr. Niecestro from Adrix Labs.

Dr. Niecestro.

DR. NIECESTRO: Good morning. I am Dr. Robert Niecestro, Senior Executive Director of Clinical Research for Adrix Laboratory. As most of you are aware, we have an FDA approved generic version of omeprazole. Prior to that I played a pivotal role in the submission and approval of rebeprazole, another proton pump inhibitor currently marketed in the United States.

I came before the committee because there are two issues that need to be addressed by this

committee. These issues are as follows. What are the effects of food on OTC omeprazole, and are potential interactions with other acid reducers understood well enough to allow for the safe and effective use of OTC omeprazole?

The proposed dozing label that was put up on the web yesterday is inadequate for instructing consumers on how or when to take omeprazole in relationship to food.

The lack of adequate information on food is nothing new to omeprazole. This was noted during the initial review of the omeprazole NDA in 1988. At that time the Food and Drug Administration requested that a definitive drug/food interaction study under fasted versus feed conditions be completed.

I have reviewed the published literature and I have concluded that this FDA requested definitive drug/food interaction study has either not been done and/or reported.

My first question to the committee is has this definitive drug/food interaction study requested in 1988 by the FDA been completed? And how do these results impact the label for OTC omeprazole and the instructions given to consumers? More importantly, even under the direction of the physician, there is

confusion on how to take prescription omeprazole with food.

Recently, and I have provided this reference in the briefing book, Gunaratnamm et al., have concluded that over 50 percent of patients taking proton pump inhibitors in a community setting were taking them incorrectly due to insufficient data on proper administration of proton pump inhibitors in relationship to food.

It is their opinion that patients have developed inappropriate dosing habits which have led to ineffective symptom control and inappropriate dose escalation.

My next question for the committee is as follows. Since current labeling for prescription omeprazole does not adequately instruct physicians, how can we expect consumers to take an OTC preparation of omeprazole safely?

Now I would also like to address some of the other label. Although the proposed label states, "Do not use with other acid reducers," it is important for this committee to remember that OTC omeprazole has been proven no better than placebo for key treatment of heartburn.

In clinical trials with OTC omeprazole

subjects did indeed use other acid reducers. There included antacids, H_2 blockers, and Rx proton pump inhibitors. Thus, I believe it is critical that the interaction of antacids, H_2 blockers, and other proton pump inhibitors be well defined and characterized with OTC omeprazole.

I'd like for the committee to know that the co-administration of antacids would alter both the disillusion rate and pharmacokinetics of omeprazole. More importantly, there is conflicting information available in the published literature on how to administer omeprazole with antacids.

The co-administration of antacids with omeprazole may not be relevant under the care of a physician but it is extremely relevant when consumers are self-administering OTC omeprazole.

More importantly, how would patients be instructed to take OTC omeprazole with antacids given the fact that there is conflicting information available from two independent studies sponsored by AstraZeneca and reported in the summary basis of approval for omeprazole.

I would like to remind the committee that in these two studies co-administration of antacids with omeprazole in one study increased by availability

but in the second study decreased it.

They sent another review of the published literature. There are no definitive datas on the effect of H_2 blockers on the disillusion rate, pharmacokinetics and pharmacodynamics of omeprazole. We have seen in clinical trials for OTC omeprazole that these agents are indeed taken and there is a great probability that more consumers will take it when they are self-medicating.

Furthermore, patients have switched from one PPI to another under the care of physicians. However, patients under the care of physicians usually do not take two proton pump inhibitors together as seen in the clinical trials conducted by the sponsor.

When two proton pump inhibitors are taken together, can they have additive or synergistic effects on the retina, thyroid, and what would be the effects on the proton pumps found in the kidneys?

In conclusion, since we do not know and fully understand drug/food interaction, drug/antacid interactions, and interactions with H_2 blockers and other proton pump inhibitors, I would like to recommend to the committee and the FDA that they not approve OTC omeprazole until these public safety issues have been fully addressed and consumers can be

properly instructed. Thank you very much.

DR. CANTILENA: Okay. Actually, we have a question for you, Dr. Niecestro. As you are heading back to the podium, I have a question for the FDA.

Is there a drug/food interaction study on file for the drug by anybody?

DR. RACZKOWSKI: I would like to introduce Dr. Suleiman Al-Fayoumi from the Food and Drug Administration. He's better pharmaceutics reviewer.

DR. CANTILENA: Thank you.

DR. AL-FAYOUMI: I would just like to note that the sponsor has submitted as part of their NDA application to the omeprazole magnesium OTC product a food effects study to evaluate the effect of food on the pharmacokinetics of omeprazole and magnesium tablets and there is significant food effect. We are probably going to recommend it be administered an hour before meals.

DR. CANTILENA: Okay. Thank you. So that is on file. Then we had a question from the committee regarding what your company has done to improve the use of Rx omeprazole.

DR. NIECESTRO: That information is confidential and I wish not to disclose it at a public meeting.

DR. CANTILENA: Okay. And some of the interactions that you talked about with sort of the other heartburn drugs would also obviously apply to the Rx omeprazole. Is that true?

DR. NIECESTRO: That is correct, sir.

DR. CANTILENA: Okay. Thank you very much.

Our next speaker is Dr. Gans. I'm sorry. There's been a change. Dr. Susan Winckler from the American Pharmaceutical Association.

DR. WINCKLER: Good morning. Thank you for the opportunity to present the views of the American Pharmaceutical Association, the National Professional Society of Pharmacists.

I am Susan Winckler, a pharmacist and an attorney, and Vice President for Policy and Communications with APhA. We are pleased with the opportunity to be here this morning.

My comments will focus on the role of the pharmacist in helping consumers navigate the use of omeprazole in the over-the-counter environment should the agency choose to approve such availability.

In the interest of full disclosure, APhA frequently partners with Federal agencies, consumer groups, the pharmaceutical industry, and others to

develop educational programs for pharmacists and consumers. The Association 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 pharmacists in all practice settings and in each of those settings we help consumers manage and improve their medication use including the appropriate selection and monitoring of prescription and OTC products.

APhA supports the transition of suitable prescription drug products from nonprescription status when supported by studies assessing the safety, efficacy, and appropriateness of such drug products for OTC use.

In the questions before the committee today this proton pump inhibitor is being considered for OTC use for the prevention of frequent heartburn. Omeprazole magnesium would be the first proton pump inhibitor to be available without a prescription.

This switch may improve clinical outcomes by expanding consumer access to a drug therapy class that is considered more effective in preventing heartburn than alternative therapies such as histamine H_2- receptor antagonists.

To determine if this product should be switched from prescription to OTC status, we urge you to consider a review of all existing therapies in the self-care market. If existing options for self-care raise questions of safety or effectiveness, the relative safety of the switch candidate increases and the risk-benefit analysis shifts in favor of OTC availability.

Decisions to classify products as either prescription or nonprescription should be based on substantial evidence of safety and efficacy in actual OTC settings. The use of the drug product in the actual OTC setting is especially important in the real-world setting of self-care.

The number of products moving from prescription to OTC status has increased markedly over the past several years, and consumers are increasingly making decisions regarding the self-diagnosis and treatment of health conditions. This is a positive trend. A challenge of this trend, however, is equipping consumers with information to help them select and use those products appropriately. This is an area where pharmacists can help.

As pharmacists we are in the ideal position to help consumers select an OTC medication

when appropriate and help monitor use of the product. Pharmacists can and do play and role in help consumers use OTC products for the prevention and treatment of frequent heartburn.

We educate patients about heartburn and more serious conditions such as GERD, ensure that patients are appropriate self-treatment candidates, assist patients with appropriate products selection, and refer patients with symptoms that may suggest a serious condition to a physician.

We also work with patients to ensure that they understand how to use the product, how often to take the medication, what dose and for what duration, and can suggest lifestyle modifications to help lessen the occurrence and severity of symptoms.

The dynamics of the same medication potentially being available for one indication in the OTC environment and other indications in a prescription environment will be challenging. The challenge, however, is not new.

Histamine H_2-receptor antagonists have been available for years in both prescription and nonprescription form. As I described earlier, pharmacists assist patients in deciding whether they should use a nonprescription product for short-term

relief of heartburn or whether a consultation with a physician is warranted to determine of a more serious chronic condition exist.

Our ability to manage the use of a product like omeprazole in a dual prescription and nonprescription environment will be directly related to the amount of information available to pharmacists.

The product sponsor must provide product labeling that clearly delineates when OTC use of the product is appropriate and directs consumers to a healthcare professional when use of the product falls outside of labeled parameters.

Additionally, an educational campaign to equip pharmacists with the proper tools to identify and select OTC therapies for frequent heartburn will be needed.

While most OTC products are purchased at the pharmacy, a recent survey showed that mass marketers such as supermarkets and discount stores without pharmacies are gaining a larger share of the OTC market. In these environments consumers make OTC decisions without the assistance of a healthcare professional. The lack of access to a pharmacists or physician places even greater responsibility on the consumer for interpretation and understanding of drug

labeling and appropriate use of medications.

Two types of studies are particularly valuable in determining whether there is sufficient evidence to reclassify prescription products to OTC status, OTC label comprehension and actual use studies. It is out understanding that the product sponsors have conducted several label comprehension studies since the agency first considered the switch in October 2000 and adjusted the labeling accordingly.

In conclusion, APhA recommends that the agency consider the real world use of omeprazole magnesium in the OTC environment, existing OTC products available for heartburn, the risks and benefits of increasing access to the product, and the ability of consumers to appropriately select and use the product without a learned intermediary. APhA supports the transition of this product to OTC status pending the outcome of this review by the FDA.

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

DR. CANTILENA: Okay. Thank you very much.

Our next speaker is Dr. Michael Wolfe, Boston Medical Center. Prior to his talk Dr. Titus has a conflict of interest statement that she will

read.

DR. TITUS: During the opening statement that addressed conflict of interest it was announced that Dr. Michael Wolfe was recused from participating in the meeting as a federal employee. He has asked to participate in the open public hearing as a member of the public.

We made the decision that he could participate in the open public hearing because we feel that the advisory committee members and the public are entitled to hear all sides of an issue and we do not want to be seen as suppressing or censoring any perspective.

The Advisory Committee Members and the public should take into account the recusal by FDA in evaluating his comments. Further, as we do for all participants in the open public hearing, Dr. Wolfe has been asked to disclose any financial interests he may have in the matter before the committee.

We specifically advise all open public hearing participants that it is important to disclose financial relationships such as being an investigator, consulting, and stock ownership with the sponsor and with any of the competitors. Thank you.

DR. WOLFE: Thank you for the opportunity

to speak. As Dr. Titus said, I am actually Chair of the Advisory Board for GI Drugs and recused because I have invented what is considered a competing agent for treating episodic heartburn. I'm the inventor. I'm not the owner. It's been licensed. I have no say in what happens with this but I do receive royalties for this.

I'm presenting Professor of Medicine at Boston University School of Medicine and Chief of the Section of Gastroenterology at Boston University and have worked there for the last 23 years.

I'm going to present data primarily on some work we have recently completed in my laboratory which has been submitted for publication. I received permission from the Journal to present this information without jeopardizing a chance of being accepted.

Before I do so, I just want to briefly mention and just follow up on some of the questions about appropriate use. I'm not sure if you understand why appropriate use. Just very briefly, PPIs are designer drugs which are designed specifically as pro-drugs and require activation. That activation occurs after eating a meal.

The food situation is quite significant

and there are studies in H_2 blockers in several animal species showing if you use an H_2 blocker and PPI at the same time, PPI doesn't work at all.

Now, I just also want to show you real world use. This is a study that we published. Only one slide is published in the American Journal of Medicine October 15, 2001. This is after several years of frustration of having patients who failed PPI therapy and decided to do a study to see why they did.

We surveyed physician to see how they use the drugs. The results are actually kind of astounding. Despite all the package inserts, instructions and numerous lectures, the fact of the matter is these drugs are designed to be taken before breakfast, before the first meal of the day.

In fact, nongastroenterologists prescribe it before breakfast in less than 30 percent of the cases. It is unlikely, in my view, that nonphysicians, consumers, would do a better job than physicians with 13 years of experience with this drug.

Gastroenterologists did better but still 3 percent incorrectly prescribed these drugs before bedtime and said it didn't matter. It does matter and all studies have been done where the drug is used very specifically.

Now I'll move on to what I'm supposed to be discussing and that is safety issues. Safety issue specifically is that PPIs are extremely potent agents, especially with certain ethnic groups which have not been studied very extensively.

For example, in Asian populations these drugs in 30 percent of the population can inhibit acid secretion for days with one dose. That hasn't been studied really.

What happens when you eat a meal? This is an introduction to what we'll be talking about, when we eat a meal the different phases of acid secretion and the two important phases of the gastric phase when food actually enters the stomach. There are three primary aspects for acid secretion. Part of the stomach extends which causes the transrelease of acid.

The protein content also intragastric pH. The pH goes up when we eat a meal. That is very important because that causes the release of gastrin. pH is clearly the most important of the three when gastrin is released and that accounts for 92 percent of the response during the gastric phase.

This causes increased acid secretion which eventually after the buffering capacity is diminished, pH goes down. We have release of another hormone and

gastric release is turned off. The classic physiological negative feedback loop. That's normally how all our bodies function.

If we turn off acid secretion, we have what is called a vicious cycle. Gastric release goes up and continues to go up in certain individuals. Is this a problem in the acute phase for 10 days? No. The fact of the matter is that people are used to using PPI for the last 13 years they read the label and it says 10 days.

In the real world what people end of doing is taking it and ignoring it and not reading the label. They will take it continuously. What will happen in this situation is 27 percent, one in four people, have elevated serum gastrin levels.

But why worry? You can't make acid. That's correct but gastrin does have other properties. This is a patient, a fairly typical patient. We'll see this fairly commonly. This is a patient who has these multiple little bumps, little polyps.

Initially when omeprazole was first presented to the FDA and actually presented for use around the world, there was a lot of concern because of these little bumps, these little polyps, irritants. As a result, actually omeprazole carried a warning

until 1995 because of these. Now some years later they are saying forget the warning and we'll put it over the counter.

These bumps actually never concerned me because these are benign tumors both in humans and in rodents which go away with cessation of therapy. There are other issues. Gastrin is a trophic hormone. It is trophic embryologically and during adult life as well with abnormal states.

What people have done in the past is they have looked at serum gastric levels and tried to correlate serum gastric levels in 100 patients to see if there is a correlation. Those studies don't really cut it. You need a large population. This is the largest they ever published, over 100,000 individuals. I'm going to quote to you the conclusions.

"...a gastrin level above normal was associated with increased risk for colorectal malignancy (odds ratio, 3.9; 95% confidence 1.5-9.8). If this association is causal, 8.6% of colorectal cancers could be attributed to high serum gastrin level. Conclusion: Hypergastrinemia is associated with an increased risk of colorectal carcinoma."

Before I go any further, gastrin doesn't cause colon cancer. It causes preexisting conditions

to get worse. This is actually a cascade of how colorectal cancer develops. You have benign abnomas which then turn to carcinoma.

This transition from here to here has to do with the rate of proliferation. Any proliferative agent will make that rate occur quicker. Gastrin is one such agent. In fact, these cancer cells make their own gastrin and make their own receptors because they are parasites which want to grow. They use whatever they can to grow. This is the case with gastrin and colon cancer.

As far as reflux, I'm going to do this just really quickly because we're talking about reflux disease here. Heartburn is a manifestation of reflux disease. The disease is reflux, the symptom is heartburn. If you have heartburn two or three times a week you have mild GERD but it is GERD nevertheless.

It appears monthly in 40 percent of individuals in this country. Weekly 15 percent of the people will say they have heartburn and 7 to 10 percent of people in this country have heartburn every single day. That is why we are here.

In most, GERD is a nuisance. Ten to 20 percent develop complications. Three to 7 percent have Barrett's Esophagus. One percent of people

endoscope for different reasons. Cancer of esophagus is the fastest growing cancer in the U.S. for unknown reasons despite the best GERD therapy ever available.

There are phenomenal drugs as far as treating reflux disease. Complications may occur without severe symptoms because of a poor correlation between symptoms and what the esophagus looks like.

These are the data looking at esophageal cancer in this country published by the Mayo Clinic. Back when I was training the most common cancer of the esophagus in the western countries was squamous which has come down in the prominent oil producing countries and places where hot beverages are consumed now. The fastest growing cancer is endocarcinoma of the esophagus, Barrett's Esophagus.

It is perplexing that the incidence of this neoplasm has increased dramatically during the very period in which highly effective acid-reducing therapies have provided symptomatic relief and healing in those individuals with mucosal injury due to the erosive effects of acid and other gastric contents.

This is what the esophagus is supposed to look like. This is a normal esophagus where it is dark because -- excuse me because the gastroenterologist can explain this and I'm not a

gastroenterologist.

This is the lining of the stomach. The stomach is an amazing organ. In my view the most important organ in the body. The reason it's amazing is because it will withstand the effects of such potent hydrochloride acid that would eat a hole in a piece of paper if you took it out. The stomach withstands that acid very, very nicely.

The lining of the esophagus is different. It does not tolerate acid very well at all. What happens sometimes for unknown reasons is this. This is not a 45-year-old white man which we generally consider Barrett's to occur. This is a 32-year-old woman who has Barrett's Esophagus.

You can see the dark lining is extending upwards. Here is a squamous lining. This is Barrett's. Barrett's is a conversion of the esophagus from the squamous lining to columnar lining. Why it happens no one knows. If I can be tautological for a second, what is happening is the esophagus is saying, "I cannot deal with this acid anymore. I'm going to change my lining to be able to withstand the effects of acid."

That's fine and dandy. It's becomes an intestinal type metaplasia. Metaplasia means "changed

growth." This data was published in 1997 showing 1 percent of people with Barrett's will convert to cancer. More recent data suggest 1 in 200, 1 in 250. Nevertheless, one in 200 or 250 is quite significant.

Mostly importantly is we have no evidence at all that treatment with any agent, surgical treatment or medical treatment will alter this conversion. We did a study recently to determine whether functional gastrin receptors are present on esophageal adenocarcinoma cells. These are human cells. Where gastrin is present, could it actually be participating in this increase in esophageal cancer.

We used SEG-1 cells which were obtained from David Beer at the University of Michigan. They were derived from a human with adenocarcinoma of the esophagus. We actually have two other humans with very similar results. I'm going to show you the SEGs of the most dramatic results.

Again, they are derived from a human with esophageal adenocarcinoma in association with Barrett's. We used alpha and gastrin. I can't go into detail again but there are other forms of gastrin which we now have data emerging where the precursor gastroms causing the exact same effect that you will see here.

This is PCR and I'm not going to explain PCR to you. This looks at the presence of different genes being expressed or being present. These are actually rat adenocarcinoma cell lines which have the gastrin receptor.

These are the SEG-1 cells of humans. Here is actually Barrett's Esophagus which you see. We have not investigated this further yet. We actually found this in a patient with Barrett's, that the receptor is indeed present.

We actually confirmed this with analysis showing this in human colon cancer, human gastric cancer. These gastrin receptors are there because they want to grow. They like the gastrin to grow. We also did a class of binding studies. These are fairly visual studies. This is confocal microscopy.

DR. CANTILENA: Excuse me. You've hit your time so if you could wrap it up, please.

DR. WOLFE: I have two more slides. This basically shows you gastrin is indeed present. It is bound to the receptor and internalized. These are control cells not showing it. Most importantly the cells grow. They do proliferate. These are two different assays. These are counting assays and MPT assays. They grow in a dose dependent fashion and

inhibit with an antagonist. This is showing the signals through the regular pathways.

My conclusion is the following. From the study the presence of functional gastrin receptors and esophageal adenocarcinoma. This raises the possibility hypergastrinemia associated with proton pump inhibitor therapy may stimulate the proliferation of preexisting esophageal adenocarcinoma.

Thank you for the opportunity to speak.

DR. CANTILENA: Thank you very much, Dr. Wolfe. I have one question if you will stay at the podium. The question is is there any evidence that the use of PPIs increases the risk of developing like esophageal issues that you have shown?

DR. WOLFE: This is the very first study that demonstrates it. As far as actually causing it, there is no evidence that what we are seeing is association that the occurrences continue to increase despite the value of the therapy. There is absolutely no evidence to show that PPIs do cause endocarcinoma of the esophagus.

DR. TITUS: In addition to the open public hearing speakers that we just heard from, the agency received three statements from organizations that could not participate today. They are available in

our book that is out on the table and the committee members have them in front of them. We received a statement from Wellpoint, from APhA, and from the American Gastroenterology Association.

DR. CANTILENA: Okay. Thank you, Sandy.

We will now move to the sponsor presentation from Procter and Gamble. If I could introduce Dr. Keith Triebwasser who will start off and then introduce other members of his team.

DR. TRIEBWASSER: Good morning, Mr. Chairman, ladies and gentleman of the Advisory Committees. I'm Keith Triebwasser with Procter and Gamble. We want to thank you for the opportunity to come here today and discuss the Rx to OTC switch of omeprazole for the prevention of frequent heartburn symptoms.

Some of you may recall that we came before the Joint NDAC/GDAC Advisory Committees in the fall of 2000. At that time it was noted that we needed to define a suitable target population and labeling that were congruent with our data and was a safe and effective use of omeprazole by this population.

Since that time we have worked with the FDA to identify this target population and to develop new OTC labeling. We have conducted label

comprehension and actual use studies with this new label.

We are here today to show you how these data support our proposed OTC label and to show you that the known benefits of omeprazole will outweigh any potential risks associated with its use in the OTC setting. Our presentation will address the questions posed to you by the FDA.

Our OTC target population is those people with frequent heartburn defined as heartburn symptoms two or more days a week. This is roughly 40 million people in the United States. Their heartburn affects their daily lives.

It affects what they eat, it affects what they can do at work and at leisure, and often their sleep. It's not surprising that the goal of people with frequent heartburn is to prevent these symptoms rather than to try and treat each occurrence.

Right now most people with frequent heartburn 77 percent of them are using OTC medications. These medications are not indicated for the prevention of frequent heartburn. The OTC medicines they use are antacids and H_2-receptor antagonists, and they frequently use these together.

Most people with frequent heartburn aren't

satisfied with the OTC medications they are taking. In fact, only 19 percent say they are completely satisfied with the heartburn relief they achieve with over-the-counter medications.

Just why is satisfaction with current OTC so low among people with frequent heartburn? One of the reasons is the current OTC therapies are not well suited to prevent frequent heartburn symptoms. The pharmacology of these OTC products limits their effectiveness against frequent heartburn. The duration of action is limited and acids only last one to two hours and H_2-receptor antagonists only last eight to 12 hours.

As a result of these limitations, these medications lack all-day efficacy. Often more than one dose is needed to control heartburn and people with frequent heartburn symptoms find themselves using these therapies repeatedly, often without complete satisfaction, or without adequate acid control. OTC omeprazole can be the solution these people are seeking.

Omeprazole is ideally suited for the prevention of frequent heartburn symptoms. Simply stated, omeprazole has the right pharmacology to meet the unmet needs of this target population. The

mechanism of action of omeprazole provides for prolonged acid suppression which reaches a maximum at three to five days of dozing.

The prolonged acid suppression means that a single daily dose prevents heartburn symptoms for 24 hours. This onset of action profile and the long duration of action of omeprazole match very well with the needs of the target population and they are ideally suited for the prevention of symptoms.

In addition, omeprazole has an excellent safety profile. This drug has been marketed for 15 years in more than 125 countries with more than 450 million patient treatments. This extensive experience with this drug has revealed no safety concerns.

Since our previous advisory committee we've had several productive discussions with the FDA and have developed a label that we think is simple, direct and, as you will see, understood and adhered to by the consumer. This label provides clear instructions on how to select and use the product and what course of action to take if symptoms continue or return.

As I have mentioned, we have identified a specific target population and an indication that are appropriate for OTC omeprazole. We believe omeprazole

should be available over the counter at 20 milligrams, the current Rx dose. This dose provides superior acid suppression and shows both clinical and statistical significance in our efficacy trials.

The directions for use call for one tablet a day taken in the morning. This is the dozing in our clinical efficacy trials and ensures 24-hour prevention of frequent heartburn.

OTC omeprazole should be labeled to be taken on consecutive days. This is consistent with both the pharmacology of omeprazole and with the needs of the people with frequent heartburn to prevent heartburn symptoms from occurring.

We believe the OTC label should specify that this regimen be 14 consecutive days. The 14-day regimen on the OTC label is a conservative application of the current clinical guidelines for omeprazole use. It is also an appropriate period after which people should be directed to see a doctor before continuing to use omeprazole.

Our actual use study demonstrates that people understand and comply with a 14-days label. This is the duration of our clinical trials which support our application. We have included the instructions to see a doctor if warning signs of a

more serious conditions are present.

We have been very clear that if symptoms continue or return, to seek physician direction before continuing to use the product. Today we will show you how omeprazole properly labeled will be safely and effectively used in the OTC setting.

With this as background, let me just take you through today's presentation flow. First, Dr. David Peura from the University of Virginia will provide his views on how OTC omeprazole can fill a crucial gap in existing heartburn therapy and how this fits with current clinical practice.

Dr. Doug Bierer will represent the results of the efficacy program, the results of the study showing that consumers used the product appropriately and according to label instructions.

Dr. Douglas Levine and Dr. Nora Zorich will discuss product safety and safe use of omeprazole in the OTC setting. Their presentations will address the risk benefit analysis for individuals who may chose to use omeprazole chronically without physician involvement.

Finally, I will summarize how the data support the safe and effective use of OTC omeprazole for the prevention of frequent heartburn symptoms.

Just a minor housekeeping note before we start. Please note there is a number in the upper right-hand corner of each slide. If you will just keep note of that number, it will help us in any follow-up questions and answers that you have.

Let me introduce Dr. Peura.

DR. PEURA: Thank you and good morning. As a practicing gastroenterologist for almost 30 years, I have treated thousands of patients with all kinds of heartburn. My clinical and research experience actually extends back to the BC era, before cymetadine, and I don't think I'm a dinosaur.

I've been involved in the evolution of all classes of heartburn medicines from the 1970s when we used to dispense the antacids by the caseloads to the 1980s when I was involved in the early trials of the H_2-receptor antagonists.

Finally, the 1990s with the latest generation of heartburn medicines the proton pump inhibitors, or PPIs. Today PPIs are the class of drugs that my GI primary care colleagues and I most frequently prescribe.

Because of their unique pharmacology and duration of action they are by far and away the preferred medication for the prevention of frequent

heartburn.

My purpose today is to give you a clinical perspective on the proposed omeprazole Rx to OTC switch. I'll talk to you about how this switch will fit into established medical practice and how it will benefit people in the OTC setting.

Now, in considering the proposed switch of omeprazole to OTC, first it's important to understand the condition of frequent heartburn. Just as the severity of heartburn symptoms ranges from relatively mild to very severe, frequency of heartburn varies as well. Some people get heartburn only once in a while, maybe when they eat a pizza.

Now, omeprazole is probably not the right drug for them because they can get immediate relief with current OTC products like the antacids or the H_2s. Larger numbers of people get heartburn two or more times a week with varying degrees of severity.

Some of them have this frequent heartburn every week and some of them only get it intermittently. It's a very common condition. There is currently no effective over-the-counter option to help these people prevent their symptoms.

The H_2s just don't last long enough and antacids just aren't strong enough. While these

heartburn medications are adequate for treating symptoms of occasional heartburn making you feel better after that pizza, clinical experience has taught us that only PPIs can prevent the symptoms of frequent heartburn. We're talking about 40 to 60 million people out there.

I don't think all of these people with frequent heartburn need to see a doctor before beginning treatment. I do think with proper OTC medication consumers can safely and effectively self-manage their symptoms including on deciding when to see a doctor.

To explain why, let's talk first about how physicians use PPIs to prevent frequent heartburn. Conservatively I would say that more than half the patients I currently see take PPIs and that would probably be also true for my GI colleagues and many of these patients have failed the H_2s.

Primary care physicians are also very comfortable prescribing this class of medicine for most of their patients with frequent heartburn. In fact, in the United States most PPI prescriptions are written by primary care physicians.

When patients come to me with frequent heartburn symptoms and there are no warning signs of

any other condition, I give them a short course of a PPI like omeprazole. Neither my colleagues nor I routinely do diagnostic tests unless a patient has severe or refractory symptoms.

In fact, few doctors would recommend initial endoscopy for a patient who complains only of frequent heartburn. This is actually what the professional societies currently recommend, a therapeutic trial before endoscopy. When I start a patient on a PPI they usually get better very quickly. I'm confident of the diagnosis and I'm simply follow their clinical progress.

This treatment approach to frequent heartburn that I've just described in the sponsor's proposal for OTC omeprazole are very consistent with current practice guidelines. In fact, the most recent published guidelines specify that therapy should be aimed at treating or preventing heartburn symptoms with acid reducing medicines. If acid reducing medicines prevent symptoms, nothing further needs to be done. Therefore, symptom management is really the first stage of patient management.

These patients are quite knowledgeable and they can recognize their frequent heartburn for what it is. They know when they need to see a doctor.

Given these factors and since symptomatic management and prevention would be the doctor's initial approach, I believe that with a safe and effective OTC medication consumers will successfully self-manage their frequent heartburn.

Let me elaborate on this. First the sponsor's proposed label educates consumers to take omeprazole for 14 days and not to take it any longer without first contacting their doctor. I remember, and I'm sure many of you do, that there was a concern when the H_2s when over the counter that people would stop going to see their doctors.

Studies show that didn't happen. People still see their physicians about their heartburn. I expect the same will be true with OTC omeprazole. In fact, the sponsor's data would suggest that consumers will follow instructions and will ask their doctors about their frequent heartburn even if they haven't done so already.

Now, undoubtedly there will be some consumers who will take the drug for longer periods of time without talking to their physician. This doesn't really concern me because it's likely that's what their doctor would have told them to do anyway.

We know that when patients with frequent

heartburn are treated with PPIs they do much better than those who are treated with any current over-the-counter medicine primarily because PPIs are more effective at reducing acid.

Some of you might have concerns that OTC omeprazole might mask or delay a diagnosis. I'm comfortable that's not going to be the case. It didn't happen when the H_2s went over the counter.

As far as masking a more serious condition, while it's conceivable, in almost 15 years of using these drugs and thousands of patients I've not seen it. In my opinion the risk benefit here is very favorable.

In conclusion, the best way to manage frequent heartburn is to prevent symptoms. Taking a PPI is the best way to do that. Doctors know that and that's why doctors use PPIs in their patients with frequent heartburn.

Certainly physicians have a role in the management of these patients but that involvement doesn't have to be intensive. This is a common condition. Consumers who have it and understand it know when they need to see their doctor.

They can safely and effectively self-manage their own frequent heartburn symptoms and I

believe they should be empowered to do so. The proposed dose and duration of therapy is appropriate, effective, and consistent with current medical practice.

From my 30 years of clinical experience I know omeprazole is safe and it works. More importantly, so to my patients with frequent heartburn. Thank you very much.

DR. BIERER: Good morning. Thank you for the opportunity to come here to present the results of our clinical efficacy and our consumer behavior program that supports the use of omeprazole for the prevention of frequent heartburn symptoms.

Our program consist of efficacy and consumer understanding and behavior studies. First, pivotal studies that shows omeprazole prevents the symptoms of frequent heartburn for 24 hours and over a two-week period.

Second, consumer understanding and behavior studies show that consumers understand the product label and they use this product appropriately in a naturalistic OTC setting. Our entire program supports that the product is efficacious and the consumers will use omeprazole safely and according to the label directions.

We conducted two well-controlled efficacy trials in which we evaluated the efficacy of omeprazole magnesium for the prevention of the symptoms of frequent heartburn over a 14-day period. As you know, these studies were presented at a previous advisory committee meeting and they support our proposed dose and our dosing duration.

The study population included subjects who had heartburn symptoms two or more days a week and did not have prior physician diagnosis for GERD or erosive esophagitis. The subjects in the study were instructed to take one tablet every morning for 14 consecutive days. The end points that support our proposed label are the percentage of subjects who are heartburn free after the first dose of the product and a percentage of heartburn free over 14 days of consecutive dosing.

Let's look at the results of these studies. This slide shows the percentage of subjects who were heartburn free for the entire day over 14 days of consecutive dosing. In both studies we achieved our primary endpoint. That is, the prevention of heartburn symptoms for 24 hours after the first dose of product.

A higher percentage of people taking 20

milligrams of omeprazole were heartburn free as compared to placebo. As also can be seen from this graph, heartburn prevention increases over the first few days of dosing.

This is consistent with the pharmacology of the drug and this prevention effect remains consistently high over the 14 days. The effect is both clinically and statistically significant for both studies on day one for day 14 and across all 14 days.

In summary, our efficacy studies show that 20 milligrams of omeprazole provides clinical and statistically significance in the prevention of heartburn symptoms. The study supports our proposed OTC label indication which is the prevention of the symptoms of frequent heartburn for 24 hours. It supports our proposed dose of 20 milligrams and the label's direction to take one tablet in the morning for 14 consecutive days.

Now let's look at our consumer understanding and behavior program. For our OTC target audience of people with frequent heartburn, our program objectives were to demonstrate the consumers correctly self-selected, this was a product that they were willing to use, they understood how to use the product, and they adhered to the product warnings.

In our consumer understanding and behavior program we conducted two types of studies labeled comprehension and an actual use study to understand how the general population will use this product in a naturalistic OTC setting.

All of these studies met our objectives in that the vast majority of the people understood the product label, they used the product appropriately, and they adhered to the warnings.

In our first labeled comprehension study, we recruited 684 subject from 12 geographically and social economically diverse sites across the U.S. This study population included people with infrequent or no heartburn, people from our OTC target population of people with frequent heartburn, low literate frequent heartburn people who had less than an eight grade reading ability as measured by the REALM test which evaluates the understanding of medical terminology, people with potential drug-drug interactions, and finally those who are pregnant or nursing.

In general all five groups scored very well on label comprehension. Let's take a closer look. First, let's look at subjects with infrequent or no heartburn. Seventy-eight percent with

infrequent or no heartburn correctly chose this was a product they should not use for episodic or acute heartburn of one day a week or less.

Ninety-nine percent of frequent heartburn people correctly chose this is a product that they could use. These data demonstrate a high understanding of who should and should not use the product.

We were also interested in low literate subjects' comprehension of the label. For this portion of the study we gave each person in the low literate group descriptions of situations involving either frequent or infrequent heartburn. Then we asked them whether they should use this product in this situations.

In situations involving frequent heartburn 79 percent answered correctly. In situations involving infrequent heartburn, 49 percent answered correctly. Initially these results concerned us. As you will see later, in our actual use study the low-literate group scored much higher for appropriate self-selection.

Now, let's look at how well all subjects understood the dosing directions. Here we found high comprehension of the label dosing directions.

Subjects clearly understood how much omeprazole to take, how often to take it, and to contact a healthcare professional before taking it for more than 14 days.

We also then looked at other circumstances which would require healthcare provider involvement. In our proposed label we included warning for people who have symptoms that could be mistaken for or occur with any heartburn of any severity. These include chest pain, trouble swallowing, frequent wheezing, unexplained weight loss.

It is important to note that these symptoms are not related to the use of any kind of heartburn medication. Because these symptoms can be the sign of a more serious condition, we advise people in our label to talk to their doctor about these symptoms if they have not done so already.

After testing several versions of the label, we achieved labeling which was understood by 81 percent of the people with these general warning signs. As you will see shortly in our actual use study, people were compliant with this warning.

Regarding drug-drug interactions, we would that people were much more likely to understand the nature of the drug-drug interaction when they were

shown brand names in addition to the generic drug names.

As you see, 82 percent responded correctly when shown both the brand name and the generic name as opposed to 50 percent when shown just the generic name. Because of regulatory and policy consideration, we believe it is most appropriate to discuss this labeling issue with the agency at a later date. Also, more than 90 percent of pregnant and nursing women correctly selected that they shouldn't use this product without consulting their physician.

Now, let's look at our actual use study. As you know, label comprehension studies indicate whether people understand what is written on the label. What is even more important is how people will use the product in a real world setting.

Our actual use study had three major objectives, to evaluate whether consumers correctly self-selected, whether they used a product appropriately to prevent the symptoms of frequent heartburn, and whether they complied with the label.

In our actual use study we found that consumers did correctly self-select. They used a product appropriately for prevention and they used it according to label directions. We designed our actual

use study to mimic real world purchase experience using both traditional methods and some new features.

This study was conducted at a mall kiosk which was freely accessible to subjects rather than at a clinical site. To ensure that subjects were able to correctly self-select based on the product label alone, there were no healthcare professionals on site.

There was no contact with the subjects during the use portion of the study. And, as with any OTC medication, the subjects were free to contact their doctor at anytime during the study.

We also incorporated a couple of new features designed specifically to mimic real world consumer purchase decisions. Subjects purchased the product at a realistic market price and they were free to return to the kiosk to buy additional product.

We were also very careful not to present barriers for repurchase. The kiosk was highly accessible, it was open during regular mall hours, and it was close to where the subjects lived. The subjects were told numerous times that they could return to buy additional product.

Let's take a closer look at this study. We recruited subjects through local advertising in spontaneous mall intercept at five malls across the

U.S. At the mall kiosk the subjects made a self-selection decision. That is, they had to determine whether this was a product that they could use, and also whether they were willing to purchase the product.

Our product is intended to be used for a regimen of two weeks and not to be used for more than two weeks unless directed by a doctor. It was especially important to find out whether people would incorrectly use the product on an extended basis without physician involvement.

Therefore, we made the product available for a total of eight weeks and during that time people could have bought as much product as they wanted and theoretically they could have used four courses of treatment.

Four weeks after the use period we contacted the participants by telephone and asked them whether their frequent heartburn returned and, if so, what were they doing about it.

Before I describe the results of this study, let's first look at the disposition of subjects. We approached 5,060 subjects at the mall and we asked them, "Do you get heartburn?" Of these 3,809 said they either did not get heartburn, they

were not interested in being interviewed, or the drug was not appropriate for them to use.

Of the 1,251 people who said they could use the product, 385 were not willing to buy the product mostly because they were not interested in participating in a clinical study or they wanted to check with their doctor before taking a new medication.

866 people said that this was a product that they could use and were willing to buy the product and participate in the study. This 866 constitutes are self-selection population since they not only identified omeprazole as a product that they could use, but they were also willing to buy it and use it.

When people are asked a hypothetical question, "Could you use this product," they may say yes. But in the real world the key differentiator is whether they will actually buy the product.

Now, let's look at the demographics of our self-selection population. Slightly more than half were women, 68 percent caucasian, 16 percent African-American, 11 percent Hispanic. The average age was 48 years with a range between 18 and 91 years old, and 8 percent had a low reading ability as measured by the

realm test of medical literacy.

Importantly, 90 percent of the subjects who purchased the product had frequent heartburn two or more days a week. This indicates that our label is well understood by our intended OTC target population. More than 90 percent of the people said that they used OTC medications to control their symptoms and 40 percent reported using prescription medications.

Now, let's look at whether these people correctly self-selected. As I will show you, 81 percent met all six self-selection criteria.

These criteria, which are specified on our label, include heartburn two or more days a week, greater than 18 years of age, not allergic to omeprazole, not pregnant or nursing, no general warning signs, and no drug-drug interactions as listed on our label.

In order to correctly self-select for this trial, subjects had to meet all six of these self-selection criteria. That is, if they did not correctly select any one of these answers correctly for the criteria, they were counted as a self-selection failure.

Again, of the 866 people who said they could use this product and wanted to buy the product,

81 percent met all six self-selection criteria. When we look specifically at the low-literate people, we found that almost 70 percent met all six self-selection criteria.

Let's look at the people who did not correctly self-select. Four subjects who incorrectly selected weren't allowed to buy the product. These included three of them who were under 18 years of age and another who was pregnant. There were no subjects who were allergic to omeprazole.

However, we did allow subjects who were in these last three groups on this slide at the bottom to purchase and use the product even though we counted these people as a self-selection failure. This is consistent with FDA's guidance to include self-selection failures when the risk is minimal.

There were 82 subjects who had not talked to their doctor before the study about a general warning sign listed on the label. We found that during the trial none of these subjects had a serious adverse event.

There were eight subjects who were taking a drug listed in a drug-drug interaction section on the label. While these eight subjects did not initially contact a doctor or pharmacist, we did find

that five of them did contact the doctor about the congest use with omeprazole during the study. Again, none had a serious adverse event.

Finally, there were 86 subjects who had infrequent heartburn. Half of these people took the product in compliance with the 14-day labeling and the other half took it sporadically as you would expect for someone with infrequent heartburn. None of these people with infrequent heartburn exceeded 14 doses.

Now, let's move to look at the use and repurchase phase of the study. Of the 866 people in our self-selection population, 96 did not return a diary despite several contacts.

Four subjects withdrew consent and eight were not allowed to purchase product. This includes the three subjects I mentioned earlier who were less than 18 years of age and the one pregnant woman.

There were also four others who had participated in a previous use study with this product. But importantly, 90 percent of our self-selection population, that is 758 people used the product and returned the diary.

Our use directions call for taking one tablet per day. Let's look at whether people complied with this use direction. Here we found excellent

compliance with the dosing directions. Ninety-six percent of the subjects took no more than one tablet per dose and 91 percent of the subjects took only one tablet per day. Again, people clearly understood these label directions.

One of our key questions is whether people with frequent heartburn would take this product as a regimen for 14 consecutive days. In our protocol, we defined compliance to the 14-day dosing regimen based upon two criteria.

First, they had to take between 80 and 100 percent of the product and take it over 14 days plus or minus three days. This is a range of about 20 percent for the days. That is, they had to take between 11 to 14 doses of the product and take it within 11 to 17 days.

This criteria is similar to the industry convention and epidemiological conventions of patients taking at least 80 percent of study medication in the clinical trial, and is also consistent with the long-lasting pharmacology of the drug.

The second criteria was if a subject took more than 14 doses of a product, that is, they took even one more dose than 14 doses, they had to consult with their doctor in order to be defined as compliant.

With this definition in mind, let's look at how people were compliant with the 14-day regimen.

This slide shows the compliance of the 14-day regimen of all 758 people who used the product and returned the diary. Seventy-nine percent of the people were compliant. That is, they took 11 to 14 doses and 11 to 17 days, or they contacted a doctor if they exceeded 14 doses.

Also as mentioned in the FDA briefing document, 64 percent of these people took exactly 14 doses in 14 days. These data demonstrate high compliance with a dosing regimen of 14 days and also use of this product for the prevention of frequent heartburn.

Nine percent of the people took the right amount of drug. That is, 11 to 14 doses, but they took it over a longer period if time, greater than 17 days. An additional 9 percent of the people took fewer than 11 doses. As expected, many of these people had infrequent heartburn.

Note that none of these group of people, this 18 percent took more than 14 doses of the product. We also saw that fewer than 1 percent took multiple daily doses of product. There were only three of these people and none of them exceeded three

doses per day, and also none had a serious adverse event.

We also found that only 3 percent of the subjects took more than 14 doses without healthcare professional contact. It is important to note that 75 percent of these people had either talked to their doctor about their heartburn before the study, or soon after the study ended.

In summary, the label was clearly understood. People understood that they were to use this product for the prevention of frequent heartburn symptoms, and they achieved high compliance with the dosing directions.

Now, as I explained earlier, four weeks after the study ended, we wanted to find out whether people's frequent heartburn returned and, if so, what they did about it. We were able to follow up by phone with about 85 percent of the people who used the product and returned the diary. Forty-three percent said that their frequent heartburn had not returned.

Of those who said their frequent heartburn had returned, 8 percent were not using any medication, 22 percent reported taking antacids, 9 percent reported taking an OTC H_2-RA, and 3 percent reported taking a combination of both antacids and H_2-RAs.

Finally, 15 percent returned to a previous Rx medication or started a new prescription. This level of physician involvement is consistent with the habits and practices we have found of people with frequent heartburn.

Our actual use study showed that consumers appropriately self-selected, they understood the label directions, and they took the product as on a regimen basis for the prevention of frequent heartburn. Finally, they used a product in accordance with label directions.

In summary, our efficacy and consumer behavior data supports our proposed label. The efficacy data supports our indication for the prevention of the symptoms of frequent heartburn for 24 hours. It supports our proposed dose of 20 milligrams and it supports our dosing directions to take one tablet in the morning for 14 consecutive days.

Our consumer understanding and behavior program shows compliance with these use directions and general adherence to the label warnings when this product is used in a naturalistic OTC setting. Thus, we have demonstrated that our proposed label, our efficacy data, and the consumer's ability to

understand and use this product safely and appropriately are all congruent.

DR. LEVINE: Good morning everyone. I would like to present a perspective, perhaps another perspective, on safety issues related to over-the-counter use of omeprazole.

One type of safety consideration is product safety. This is defined as adverse events occurring in relation to product use during the short or the long term.

Omeprazole has a excellent safety profile. The product related adverse event profile is very well established based on data from clinical trials with the prescribed product, post-marketing surveillance with the prescription product, as well as the OTC clinical trials.

As you recall, the most common adverse events are reversible symptomatic side effects including things like headache, diarrhea, and abdominal pain. This profile of omeprazole makes it acceptable for over-the-counter use.

The use of omeprazole is intended to be short term as indicated on the proposed label instructions. However, if any unintended long-term over-the-counter use were to occur without medical

supervision, the product adverse event profile for the situation is considered acceptable based on the extensive experience with omeprazole in the prescription setting.

Another type of safety consideration would include potential consequences of consumer behavior involving long-term use of the product without medical supervision but such consequences would not be directly linked to omeprazole.

This type of safety issue involves considerations of medical diseases other than acid reflux disease, as well as of the natural history of acid reflux induced esophageal damage which is not completely understood today from an epidemiologic perspective.

Again, the sequelae of these diseases are not directly linked to omeprazole. First, use of the over-the-counter product for alarm symptoms such as these would most likely be self-limiting because these symptoms would not be expected to subside with omeprazole use.

The proposed label instructed not to use the product and to seek medical attention if these symptoms are present. However, there are a variety of conditions with symptoms that could certainly respond

to omeprazole and might lead to some behavior involving long-term use without medical supervision despite the label instructions.

The most common of these would be non-neoplastic upper GI conditions resulting from acid peptic injury. These include esophageal erosive disease or peptic ulcer disease involving the duodenum or the stomach.

Such abnormalities, though, would be well managed with chronic omeprazole therapy with little chance of adverse consequences. It is important to address medical diseases that include either overt malignancy or conditions that predispose to malignancy of the upper GI track.

Individuals with cancer of the esophagus or of the stomach might have frequent heartburn. However, these tumors more typically produce different symptoms such as dysphagia, nausea, vomiting, early satiety, and weight loss which do not respond to treatment with omeprazole and would likely led the consumer to seek medical attention.

Unfortunately, these types of tumors are commonly diagnosed as part of the very first medical presentation for medical care. This suggest that these diseases commonly evolve without producing

significant heartburn or other symptoms during their precancer stages.

Additionally, in endoscopic survey studies of individuals with heartburn, cancer of the esophagus or the stomach is rarely identified.

Another area of concern is a condition associated with cancer risk and this is Barrett's Esophagus. Barrett's is a complication of chronic acid reflux disease with resulting esophageal damage. While Barrett's Esophagus is common, its progression to esophageal adenocarcinoma is unusual.

It is, in fact, the inconsistent correlation between frequent heartburn and the present of Barrett's plus the rarity of progression from Barrett's to esophageal adenocarcinoma that makes it difficult for the medical community to manage this risk. If desired by the advisory committee, we can provide additional data on this topic during the question and answer period or this afternoon's discussions.

In the context of over-the-counter treatment of heartburn, available data showed that omeprazole is, in fact, a neutral factor. It does not increase cancer risk and it does not reliably induce regression of Barrett's Esophagus.

To summarize the current situation on heartburn and esophageal adenocarcinoma, the increasing incidence of esophageal adenocarcinoma in the United States since the early 1970s is not related to acid reducers but research continues to evaluate many of the factors that may contribute to this rise in incidence.

Patients afflicted with esophageal cancer generally present without a prior history of heartburn of a prior diagnosis of Barrett's Esophagus. The status of esophageal adenocarcinoma in 2002 is as medically challenging as it is sobering.

Presently the incidence rate for esophageal adenocarcinoma is about the same as the mortality rate, again reflecting the fact that these cancers are discovered at late incurable stages without antecedent clinical signals that might lead to diagnosis of an earlier stage cancer or its precancerous precursor.

There is no evidence to suggest that acid reducers are masking any signals of these diseases. Fortunately, the development of this cancer is rare among individuals with heartburn or among those with documented Barrett's Esophagus and omeprazole specifically does not increase the risk of this

cancer.

In conclusion, I've tried to frame today's discussions on safety related to over-the-counter omeprazole use. The product related safety profile of omeprazole is acceptable for over-the-counter use. The natural history of acid reflux damage to the esophagus can involve rare serious consequences. However, omeprazole does not directly increase the risk of esophageal adenocarcinoma.

Based on the overall safety considerations I have presented today, omeprazole is acceptable for over-the-counter use. Thank you for your attention to my remarks. I would like to introduce Dr. Nora Zorich, my medical colleague, who will continue the sponsor safety presentation.

DR. ZORICH: Good morning. Thank you, Dr. Levine.

I'm going to take a few minutes to settle down here and address in more depth the question of whether there is any concern what the long-term use of omeprazole without physician involvement.

In order to do this, I'm going to consider three key factors important in the benefit risk assessment. First, we'll look at data that provides insight into what people do now and what they might do

in the future if omeprazole was available over the counter. I'm going to specifically address what proportion of consumers might use the product on a more regular basis.

Then I'll discuss data that examines physician involvement by people with frequent heartburn and specifically address the concern that once omeprazole is available, people with heartburn won't seek the care of their physician.

Finally, I'll recap the issue of potential risk and discuss the known benefits that might result for consumers who use the product even without physician involvement.

Now, before we can address how often consumers might use OTC omeprazole, I think it's worthwhile to talk a little bit about how they use it today. In order to do that, I'm going to take you all the way up to the 40,000 foot view of omeprazole use looking at a very large administrative claims database of prescription drug use.

Here is an analysis of the NDC database which collects and analyzes the prescription data from multiple managed care organizations that cover millions of lives in the U.S. We examine the drug records of almost 100,000 people who were prescribed

omeprazole for the first time in January of 2001.

Then we followed whether they had any further omeprazole dispensed to them over the next year. These data represent people who had heartburn symptoms that were significant enough that they drove them to their physician and then their physician prescribed omeprazole.

Now, let's look at this data. As you can see, about 44 percent of them were dispensed omeprazole only once in a one-year period with about 70 percent of this group of people receiving three or fewer treatments dispensed to them over a year.

Then we get down to a group that I have collected together of people being dispensed six or more treatment courses and that's about 20 percent of this group. From that perspective we can look at chronic use of those people who would be taking the drug on more days than they would not be over a year.

Chances are what we know about chronic users these would be the same people who would go on to future use on a chronic basis. That's the really big picture of omeprazole use. Let's take a step further into understanding how this drug is used and look at a population specifically diagnosed as having GERD.

Here is a study published by Bardhan. It was a randomized clinical trial in which people with symptomatic frequent heartburn were evaluated and how often they required omeprazole to control their symptoms.

The reason I selected this particular study to discuss is that in contrast to the numerous studies that have been done looking at maintenance therapy, few studies have actually examined the strategy of intermittent therapy.

This particular study is helpful in that it captures the kind of use decision behavior that you are likely to see in the OTC setting. That is, the patients going back to the clinic for more treatment if and when their symptoms returned.

The most relevant group for our discussion are those people in this trial who took an initial course of therapy 20 milligrams of omeprazole for 14 days. Then they self-managed their frequent heartburn by requesting additional courses of therapy throughout the year.

Let's look at the results. There were 704 people on this trial and 526 were available for a final assessment. Bardhan found that 72 percent of these individuals were able to self-manage their

frequent heartburn by taking additional 14-day regimens of omeprazole intermittently. Of the 72 percent 68 percent requested three or fewer treatments.

To put that in perspective, that is 42 days of omeprazole in a year. This pattern of use is actually quite similar to what was seen in that big NDC database where we saw about 70 percent of use being three or fewer treatment courses over a year.

Bardhan found that symptom control after two weeks of therapy was a powerful prognostic indicator of future need for therapy with almost 30 percent of the people requiring no further treatment if they had a good response to that first 14 days.

At the other end of the spectrum of use, only 28 percent of the study participants had ongoing symptoms which required maintenance therapy at some point during that one-year period.

Let's compare these data to our actual use trial, what you just heard from Dr. Bierer, where we found that well over 90 percent of the participants in the actual use trial purchased only one box of 14-day omeprazole during the two-month period that the drug was available.

When we contacted them three months after

they entered the study, 43 percent of them said they did not have frequent heartburn and 42 percent while they said their frequent heartburn was back, over half of them had elected to manage their symptoms simply with antacids. And 15 percent of the participants were taking a prescription therapy.

Within this 15 percent half of them had just gone back on the prescription therapy they were on prior to their participation in the study. The other 15 percent had gone to see a physician and were prescribed a prescription therapy, generally a PPI.

After three months of observation, we found that very few people had used more than the one 14-day regimen of OTC omeprazole even when they had the opportunity to purchase it.

In summary in answering my first question, you could look across these three diverse types of data and see that even in the prescription setting it's clear there is a range of use of PPIs which undoubtedly reflects the range of symptoms with only on average about 25 percent of the use being chronic. We conclude that most people won't choose to use omeprazole chronically even in the OTC setting.

Now, returning to the larger consideration of chronic use without physician involvement, we need

to ask will these people who may use omeprazole chronically see a physician. We have literature in our actual use trial to address that.

To begin with, it is helpful to review what we know about how often people with heartburn talk to their physician about their condition. Here is a publication from Oliveria who was at Cornell at the time. They surveyed more than 2,000 people with heartburn. The study was designed to capture people's understanding of heartburn, how they manage their symptoms, and importantly how often they consulted a physician.

More than 90 percent of these people were on some kind of therapy with 75 percent of them taking over-the-counter therapies. In regard to physician involvement, what the survey found was logical. The more frequent and severe people's symptoms were, the more likely they were to have seen a physician.

In fact, people with the most frequent heartburn were four times more likely to have seen a physician than those who had heartburn less than twice a week with 78 percent of the people with frequent heartburn having discussed their heartburn with their physician.

This is reassuring data and it's really

very typical of what you find in the literature and in the surveys that have been conducted by the professional societies. Relative to our discussion today is whether omeprazole's availability in the OTC market would change this consumer behavior.

Now, as Dr. Peura mentioned, this question has been asked before. The recent move of H_2-RAs to OTC status in the 1990s provides a historical perspective on this question.

We are going to look at three studies that specifically examined what happened to physician visits when the H_2-RAs became available. I take the position that this is actually a relevant comparison because even though the H_2-RAs were switched at half the prescription dose, the introduction of H_2-RAs into a world that only had antacids was a meaningful therapeutic jump.

For perspective, a study by Simon and colleagues published in the American Journal of Therapeutics in 1995 stated that 70 percent of the people who obtained only some degree of relief with antacids claimed they experienced complete symptom relief for episodic heartburn using the H_2-RAs.

Yet, as you'll see, there was no negative consequence relative to physician visits for

heartburn. Here is our first study. It's a publication from Andrade studying 2,000 people within the Fallon Community healthcare system who had a GERD related diagnosis and were receiving a prescription medication in 1994. What they found was that the yearly number of clinic visits in those patients with GERD stayed the same and averaged just under one visit per year per patient.

The second study was published by Shaw. It was a cross-sectional survey of adults in Minneapolis in 1993 which would be before the switches and again in 1997 after the switches. Within this general population the percent of people who went to the physician with complaints of dyspepsia or heartburn did not change when the H_2-RAs became available.

Finally, we took another look at a very large dataset, the MEDSTAT Marketscan Database of Administrative Claims, that covers again millions of lives. We looked at the people who had continuous coverage from the period of 1995 through '98. That's the period during the switch of the H_2-RAs.

We found that the percent of people undergoing endoscopy was not changed. And importantly, the mean number of visits for acid

related diseases was constant with a mean of about two visits per year.

So we see from these three studies we found there was no evidence that potent acid-reducing drugs kept people from seeking physician care. Of course, the question for today is would omeprazole be different. For that we can look at our actual use trial.

What was the behavior of these participants who had omeprazole available to them nonprescription? When we looked at physician contact in the study during the period of our trial, we found that on average the monthly rate of physician visits actually rose. The rate of physician contact per month was twice what it was per month in the year prior. This was in part due to the behavior of two very important groups of people.

First, we were very pleased to see that 20 percent of those consumers who are potentially harder to reach, these were people who had never before discussed their heartburn with their physician. Twenty percent of them opted to talk to a physician about their heartburn when they participated in this study.

Importantly, over 50 percent of those

individuals who took more than the 14-day regimen were in contact with their physician either during the study or when we contacted them at three months they told us that they did have a visit scheduled to discuss their heartburn.

We were very encouraged by this behavior and we believe this increased physician contact was driven in part by the label and the package insert. So from the published literature and the result of our actual use study, we see a consistent picture. The majority of people with frequent heartburn do talk about this with their physician.

People continue to see their physician even when the H_2-RAs became available. The label we propose for OTC omeprazole encourages people to go to the doctor and we believe that is important. As we saw in our actual use trial, the rate of physician visits actually increased.

Consequently, we believe that physician visits will not decrease and there is a chance that they could increase with OTC omeprazole available over the counter.

Now, while the data we have just reviewed is reassuring in that most people are not going to be using this product chronically, and those who do are

going to be the same people that are most likely to be talking to their physician, what about the product use on a more chronic basis with people who simply will not seek physician involvement? What are the risks and benefits to these consumers?

Now, let me restate before I go on to talk any further about the benefits to these consumers that our position is clear. The label advocates physician involvement for those individuals who are using the product beyond 14 days.

In considering this population, probably most of these people are going to have nonerosive disease. For these individuals if their symptoms are well managed then there is a benefit and there is little chance of any adverse consequences we've heard today.

However, it's clear that some of these people could, in fact, have some degree of erosive disease. Consequently, it's important to examine the potential benefit for these consumers.

Studies published in the literature have clearly shown that PPIs provide better healing of mucosal injury compared to other therapies. The easiest way to summarize all of that is just to look at one single publication, a medianalysis by Chiba

which I have shown one graph from that analysis.

This is a compilation of 43 studies looking at the healing of erosive esophagitis grades two to four, and it compares PPIs, H_2-RAs, and importantly placebo. I think you don't ever really see this result much but if you look at placebo after 12 weeks you get about 25 percent of healing in people not taking any therapy.

What I want to emphasize from this graph is that people taking PPIs you'll see that at two weeks there is more percent of people healed compared to even much longer treatment periods on H_2-RAs.

Importantly, considering the placebo response, when you look at the overall percent of healing due to PPIs, you can see that the vast majority of that healing actually occurs within the first two weeks.

Consequently, people who are not healed at two weeks experience only a modest benefit from any additional therapy. I think this data clearly showed that for those few people who have erosive esophagitis and choose not to be in contact with their physician, a 14-day regimen of omeprazole is going to be a much better option for them compared to any other medication that they would take over the counter.

In summary, we believe that the data in the literature, our analysis of large databases, and our actual use trials support that the majority of consumers will not use the product chronically.

Those consumer who may choose the product on a more frequent basis will do so with the involvement of their physician. Considering what we have heard from Dr. Peura and Dr. Levine, the potential risk for chronic dosing is minimal, while the known benefits are substantial.

DR. TRIEBWASSER: I would like to just briefly summarize what you have heard here today. You have heard that omeprazole will fill a critical gap in the OTC options for those people who suffer from frequent heartburn and who currently have no adequate OTC therapy to prevent their symptoms.

Omeprazole is ideally suited to meet the needs of these people for effective prevention of heartburn symptoms for 24 hours. From Dr. Peura you heard that OTC omeprazole fits into current medical practice and can be a safe and effective medication over the counter.

You heard that we have identified the right target population for OTC omeprazole. This target population is those people with frequent

heartburn. This is the population that will benefit most from omeprazole and it is the population in our pivotal clinical studies.

We have shown you that the proposed label provides clear instructions for use. The actual use study demonstrated that this label is understood by consumers and that they appropriately self-selected and used the product.

The study also demonstrated that individuals who had a recurrence of heartburn symptoms responded appropriately. This label is congruent with out proposed use of omeprazole. It brings the right target population and the right indication for OTC omeprazole together with clear use instructions and a set of clear directions for physician involvement when appropriate.

You heard that OTC omeprazole should be labeled for 14-day regimen of therapy. Our efficacy trials and actual use studies showed that people received maximum symptomatic benefit within 14 days and that they understood and complied with the 14-day label.

Fourteen days is a conservative application of clinical guidelines. It also represents an appropriate period of OTC use after

which a person should be instructed to contact a doctor if symptoms continue or return.

You also heard that 14 days of omeprazole provides healing to most of that fraction of individuals in the target population who may have erosive esophagitis. For all of these reasons, the OTC label should not specify a longer treatment period.

You have heard that some people may use OTC omeprazole on an ongoing basis without seeing their doctor. Some of these individuals may have GERD or erosive esophagitis. They will be receiving a more beneficial therapy than the medications available today over the counter. Any potential risks will be outweighed by these known benefits of omeprazole.

In conclusion, omeprazole can be safely and effectively used over the counter. Thank you for your attention. We will be glad to answer any questions.

DR. CANTILENA: Okay. Thank you very much for your presentation. What I would now like to do is actually entertain questions from the committee members to the sponsor. We will go sort of around the table. Well, actually, if there is anyone who has a question, let's just start with a show of hands and

we'll identify you.

Okay. Dr. LaMont, Dr. Davidoff, Dr. Brass, and Dr. Camilleri for starters. Please don't put your hands down after.

DR. LaMONT: I wonder if we can get some clarification on the issues that were raised regarding the effect of food and antacids and other drugs on absorption. Your briefing book states on page 28 that omeprazole is completely absorbed after oral administration.

Food, antacids, and H_2-RAs have no clinically meaningful influence on the extent of omeprazole absorption. Yet, we've heard from others this morning that there are important effects of these agents on absorption. I wonder if we can have some clarification.

DR. TRIEBWASSER: Certainly. In the Rx clinical trials for ethical reasons antacids were always allowed. These were placebo-controlled trials. We have extensive data with a prescription product where it was utilized with antacids without deleterious consequences.

As was indicated before with regard to food interactions, I'm not sure if you want to take time now but we have submitted data showing that with

the tablet formulation that is proposed for OTC use, there is really not a significant food effect. So we've done those studies, yes.

DR. LaMONT: Just a question of further clarification. You say on the extent of absorption. Do you really mean on the extent of clinical efficacy? Because we don't measure absorption clinically. The briefing book says absorption. I think you are referring to clinical effectiveness. Is that correct?

DR. TRIEBWASSER: Clinical effectiveness on the antacids with regard to food absorption. That's where we actually did those kinds of studies. I'm not sure if I'm pinpointing your question exactly.

DR. LaMONT: I'm trying to find out what clinically meaningful influence on absorption because we don't measure absorption clinically and we don't care about that. What we are really interested in is effectiveness. If I understand your response correctly, it had no effect. That is, antacids and other agents had no effect on clinical effectiveness.

DR. TRIEBWASSER: That is our belief. Yes.

DR. CANTILENA: Okay. Dr. Davidoff, please.

DR. DAVIDOFF: I have some questions about

what I guess I've been thinking of as the dog that didn't bark. The barking dog is the potential relationship between omeprazole and cancer.

In the company's materials on page 83 there's the statement that there is no evidence that there is a causal relationship between the use of omeprazole and the development of gastrointestinal cancer in humans. Dr. Levine's slides 54 and 56 say the same thing.

I am somewhat puzzled, however, because in the materials that were given to us from the 2000 hearings on omeprazole, the summary statement from the medical review by the FDA says as follows:

"Although in the general and undifferentiated population of the U.S. there is no clear tumor association with omeprazole, the possibility that there are oncogenic effects in subceptable groups exposed to omeprazole for very long periods of time has not been ruled out.

Phase IV studies (and this is in italics) to investigate the incidents of GI adenocarcinoma and other malignancies using long-term prospective or nested control cohort study designs of large numbers of exposed individuals should be established."

They base this statement on the concern

that the studies available were too short and not appropriately designed. In effect, they were saying there is absence of evidence and that is basically what the company statements have said. The statisticians are fond of reminding us that absence of evidence is not evidence of absence.

In 1930 if you asked anyone if there was a connection between smoking and lung cancer or lots of other diseases, they would say there is no evidence, but that was not because there was an absence of effect because no one had looked.

My question is has the company done appropriate prospective or nested cohort, or case control studies as suggested in the year 2000 on this aspect of safety? If they haven't actually themselves done those studies, have you at least done an exhaustive review of the literature and, if so, what did you find?

DR. TRIEBWASSER: Let me respond. I don't think the characterization of our review in any way resembles anything that has been done with the tobacco company. In fact, we have looked extensively. I would submit that the FDA position is conservative but I can review for you the nature of the data that the company is prospectively and proactively obtained over

the 20-year history of the availability of this product.

First, as you may recall, the initial target tissue of concern was the ECL cell based on animal studies. In response to obvious concerns of the study that Astra at that time conducted actually several prospective controlled studies ranging in length anywhere from two to five years.

But then also open-label observational compassionate use studies in which individuals were treated in doses as high as 40 milligrams of omeprazole and endoscoped on a regular basis to actually look at not just the gastric musocal but actually the entire GI tract.

These are data that were prospectively submitted to FDA in response to agency requests over the past few years they have actually resubmitted and reanalyzed those kinds of studies.

In addition, there's been extensive post-marketing reports that we've collected and there are certain weaknesses with those kinds of data but they are available data.

We have always complied with a prospective reporting of those, but also submitted a number of analyses looking at not only upper GI tract cancers

but pre-cancerous lesions as well as precancerous lesions and cancers of non-GI tract tissues.

Those data once analyzed did not reveal any safety signal whatsoever, although the entire marketing history of the product, and those data were submitted to FDA as well.

Response to this is that: "Yes, there is no evidence." The nature of the kinds of studies, one could argue, may not be the perfect scientific result, but this would be utterly impractical to perform.

DR. DAVIDOFF: Thank you very much. That is somewhat reassuring, although those studies are obviously very difficult to do and hard to interpret.

I have on other question. It has to do with the related issue of the potential masking of symptoms and the delay in diagnosis of GI cancer because in the data presented to us again in the 2000 material from the FDA, it was pointed out that there were in the patients taking the drug 49 cases of adenocarcinoma of the stomach occurred and, "In at least four of these cases, OMP therapy caused masking of symptoms and/or temporary healing of gastric mucosal with a one to 12 month delay in diagnosis of malignancy.

I note that this occurred in patients who,

of course, were already seeing physicians because that's where they got the prescription for the PPI. I would ask the question, therefore, wouldn't the risk for the masking of serious symptoms like PPI be somewhat greater than this in the OTC environment, particularly since we know the post-marketing reporting of such events is notoriously incomplete.

DR. TRIEBWASSER: Again, the sponsor perspective is that the screening and surveillance detection of upper GI tract cancers are amazingly difficult to do. The medical community does not know who to screen and how identify as risk populations and that we have a chance to intercede.

I think there are certainly going to be documentation of these rare instances, but the bulk that we rely on are the instructions which are going to be for limited use and certainly strongly advising that individuals in the consumer population keep their physicians in the loop.

I think that this whole area is ripe for a new investigation because I think it's just a very challenging issue even when such individuals are in the hands of physicians.

DR. DAVIDOFF: Thank you.

DR. CANTILENA: Dr. Brass.