UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

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NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

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SAFETY ISSUES RELATED TO ASA AND NSAIDs

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MEETING

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FRIDAY
SEPTEMBER 20, 2002

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The Advisory Committee met in the Maryland Ballroom of the Hilton Silver Spring Hotel, 8727 Colesville Road, Silver Spring, Maryland 20910, at 8:00 a.m., Louis R. Cantilena, Jr., M.D., Ph.D., Chairman, presiding.

PRESENT:

LOUIS R. CANTILENA, JR., M.D., Ph.D., Chairman
SANDRA TITUS, Ph.D., Executive Secretary
LESLIE CLAPP, M.D., Member
FRANK F. DAVIDOFF, M.D., Member
JULIE A. JOHNSON, Pharm.D., Member
Y. W. FRANCIS LAM, Pharm.D., Member
DONALD L. UDEN, Pharm.D., Member
HENRY W. WILLIAMS, JR., M.D., Member
SONIA PATTEN, Ph.D., Member/Consumer Representative
ALASTAIR WOOD, M.D., Member/Consumer Representative

SGESs PRESENT:

ERIC BRASS, M.D., Ph.D., NDAC Consultant

RALPH D'AGOSTINO, Ph.D.,NDAC Consultant
RICHARD NEILL, M.D., NDAC Consultant
BARRY RUMACK, M.D., NDAC Consultant
H. JAMES WILLIAMS, M.D., Rheumatologist
JOHN CUSH, M.D., Rheumatologist
JANET ELASHOFF, PhD., Rheumatologist
NATHANIEL KATZ, M.D., Anesthesiologist
PAUL B. WATKINS, M.D., Hepatologist/(GI SGE)
JEFFREY KOPP, M.D., Nephrologist
LOREN LAINE, M.D., Gastroenterologist
BYRON CRYER, M.D., Gastroenterologist
RUTH S. DAY, Ph.D., Epidemiologist/Risk Committee
MICHAEL R. COHEN, R.Ph., M.S., D.Sc., Epidemiologist/Risk Committee
STEPHANIE Y. CRAWFORD, Ph.D., Epidemiologist/ Risk Committee
MARIE R. GRIFFIN, M.D., M.P.H., Guest Speaker Consultant (Non-voting)
MICHAEL B. ALFANO, D.M.D., Ph.D., Industry Representative and Guest (Non-voting)

FDA REPRESENTATIVES PRESENT:

JULIE BIETZ, M.D.
CHARLES GANLEY, M.D.
WILLIAM GILBERTSON, Pharm.D.
JOHN JENKINS, M.D.
MIKE JOHNSON
DEBBIE LUMPKINS
JUAN CARLOS PELAYO, M.D.
JOYCE WEAVER, Pharm.D.

C O N T E N T S

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

(8:10 a.m.)

DR. CANTILENA: This is a meeting of the Nonprescription Drugs Advisory Committee. My name is Lou Cantilena, Chief of Clinical Pharmacology at the Uniformed Services University. I'll be chairing this meeting of the NDAC. We're here to discuss the safety issues related to aspirin and non-steroidal drugs.

We will start by going around the room and introducing the other members of the panel and perhaps we can start on this side with Dr. Rumack.

DR. RUMACK: Barry Rumack, the University of Colorado and the Rocky Mountain Poison Center in Denver.

DR. CRAWFORD: Stephanie Crawford, the University of Illinois College of Pharmacy.

DR. CUSH: Jack Cush, Presbyterian Hospital, Dallas.

DR. ELASHOFF: Janet Elashoff, biostatistics, Cedars Sinai and U.C.L.A.

DR. WATKINS: Paul Watkins, University of North Carolina in Chapel Hill, hepatologist.

DR BRASS: Eric Brass, Harbor-U.C.L.A. Medical Center.

DR. DAVIDOFF: Frank Davidoff, Emeritus Editor of the Annals of Internal Medicine.

DR. LAM: Francis Lam, Department of Pharmacology, U.T. Health Science Center in San Antonio.

DR. CRYER: Byron Cryer, gastroenterologist from the University of Texas Southwestern in Dallas.

DR. LAINE: Loren Laine, gastroenterologist, University of Southern California, Los Angeles.

DR. D'AGOSTINO: Ralph D'Agostino, biostatistician, Boston University in the Framingham Study.

DR. ALFANO: Mike Alfano from New York University, and I'm the ILR.

DR. CLAPP: Leslie Clapp, pediatrician, Main Pediatrics, Buffalo, New York.

DR. TITUS: Sandy Titus, CDER, the Executive Secretary for NDAC.

DR. KATZ: Nathaniel Katz. I'm a neurologist specializing in pain management with Harvard Medical School in Boston.

DR. JOHNSON: I'm Julie Johnson. I'm a clinical pharmacist from University of Florida.

DR. UDEN: I'm Don Uden, University of Minnesota, College of Pharmacy.

DR. WILLIAMS: Henry Williams, family

practice, Howard University, Washington, D.C.

DR. NEILL: I'm Richard Neill, a family physician from the University of Pennsylvania.

DR. PATTEN: I'm Sonia Patten. I'm an anthropologist and on the faculty of Macalister College in St. Paul, Minnesota.

DR. WOOD: I'm Alastair Wood from Vanderbilt University in Nashville, Tennessee.

DR. DAY: Ruth Day, Cognitive Science, Duke University.

DR. COHEN: I'm Mike Cohen from the Institute for Safe Medication Practices. We work with the USP's medication errors reporting program.

DR. GRIFFIN: Marie Griffin, internist and epidemiologist from Vanderbilt University.

DR. BIETZ: Julie Bietz, Director, Division of Drug Risk Evaluation in CDER, FDA.

DR. GANLEY: Charlie Ganley, Director of Over-the-Counter Drugs, FDA.

DR. BULL: Jonca Bull, Office of New Drugs, Office of Drug Evaluation 5

DR. JENKINS: John Jenkins, Director of the Office of New Drugs, FDA.

DR. CANTILENA: Okay, thank you everyone. We'll now hear the conflict of interest statement by Dr. Titus.

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

The Food and Drug Administration has granted waivers to the following special government employees which permits them to participate in today's discussions. They include: Byron Cryer, John Cush, Sonia Patten, Eric Brass, Ralph D'Agostino, Ralph Day and Paul Watkins.

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

The topics of today's meeting are issues of broad applicability. Unlike issues before a committee in which a particular produce is discussed, issues of broader applicability involve many industrial sponsors and academic institutions. The committee members, consultants and invited guests have been screened for their financial interests as they may apply to the general topic at hand.

Because general topics impact so many institutions, it is not prudent to recite all potential conflicts of interest as they apply to each

participant.

We would also like to note for the record that Dr. Michael Alfano is participating in this meeting as an industrial representative, acting on behalf of regulated industry. As such, he has not been screened for any conflicts of interest. FDA acknowledges that there may be potential conflicts of interest but, because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

In the event that the discussion involves any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants involved and their exclusions will be noted for the record.

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

Thank you.

DR. CANTILENA: Thank you, Dr. Titus. We'll now hear from Drs. Ganley and Gilbertson from the FDA who will open the issues for this morning.

DR. GANLEY: There are three things I'm going to touch on this morning to introduce the discussion for today. Some of it will be a repetition

of what was discussed yesterday.

First, I'm going to give a briefer overview of how over-the-counter drug products are regulated and a brief history of the OTC Drug Review. Second, I want to make some specific comments about internal analgesic drugs. And last, I will make some brief comments on today's topic for discussion: gastrointestinal bleeding and renal toxicity associated with use of aspirin and OTC non-steroidal anti-inflammatory drug products.

As I noted yesterday, over-the-counter drug products can be marketed under two regulatory mechanisms, either through drug monographs under the OTC Drug Review or under new drug applications. The drug monographs are categorized by indications, pharmacologic effect and body system affected. When marketing under a drug monograph, the manufacturer follows the conditions of use provided for in the monograph. When drugs are marketed OTC under new drug applications, they follow the same regulations that apply to prescription products.

There is one other subtle point that also differentiates the two paths individual products that are marketed under NDAs receive FDA approval; for those marketed under monographs, the individual products are not approved, but are generally

recognized as safe and effective if they follow the conditions outlined in the monograph.

The OTC Drug Review was initiated in the 1970s to review the efficacy and safety of the OTC drug products marketed at that time. Rather than review each product individually, a review process was set up to review categories of products. This is a public rule-making process that includes data collection, a review of the data by an independent drug review panel, publication in the Federal Register of a panel report with opportunity for public comment, the publication of a proposed rule with the opportunity for public comment and it concludes with the publication of the final rule.

After the final monograph is published and the effective date is specified, only ingredients that are found to be generally recognized as safe and effective can continue to be marketed for the conditions of use described by the monograph.

Today, we are going to discuss issues related to aspirin and the non-steroidal anti-inflammatory drugs. Aspirin is marketed under the internal analgesic monograph; non-steroidal anti-inflammatory drugs are marketed under new drug applications.

Once again, I want to make some important

points regarding the internal analgesic products. Consumers can self-diagnose and treat intermittent, minor aches and pain without the need for a health care provider. Serious adverse events are rare or uncommon; the majority of consumers use these products safely. The benefit of these therapies outweigh the risk associated with their use.

The availability of these ingredients in the OTC drug products is not an issue. The Agency believes that these products should remain available as over-the-counter drug products.

The subject for discussion today is gastrointestinal bleeding and renal toxicity associated with NSAIDs and aspirin. The risk for both of these adverse events is recognized with prescription dosing of NSAIDs and included in their prescription labeling; the same can be said for the professional use of aspirin. The issue for today's discussion is an assessment of the risk for use at OTC dosing.

What is somewhat unique for an OTC drug product is the existence of professional labeling. Aspirin professional labeling provides for cardiovascular and rheumatologic indications. It also provides warnings for gastrointestinal bleeding and renal toxicity and various other adverse events. This

information is not provided to consumers; the consumer must depend on the physician or health provider to provide information for these adverse events.

The proposed rule to include ibuprofen in the internal analgesic monograph was published in the Federal Register on August 21, 2002. Compared to the labeling of the current ibuprofen products, this proposal included additional warnings.

It is important to understand that manufacturers are not required to include these warnings in their products until the FDA makes a decision in the final rule. The data and comments submitted to the proposed rule and the recommendations from this Committee will influence what additional warnings, if any, are included in that final rule.

As part of the deliberations today, the Committee will consider the following issues: What are the risks for GI and renal toxicity associated with OTC doses of NSAIDs and aspirin? Should there be labeling or other risk-management measures to decrease risk and morbidity? And finally, identify areas where interventions or research may prevent events or decrease the severity of events.

And with that, I conclude my presentation and I'm going to introduce Dr. Bill Gilbertson.

DR. GILBERTSON: Good morning. Today I'm

going to briefly discuss aspirin in the OTC Drug Review and, again, I'll be commenting from selected statements that appear in the Federal Register document that are pertinent to today's discussion.

Now, aspirin is probably the most extensively written drug in the OTC Drug Review. If you ever look at the Federal Register, there's just pages and pages and pages on aspirin. And what I did was to look specifically at those warnings or statements that dealt with the GI tract and the renal area.

The Panel concluded, back in the 1977 report, that aspirin was safe and that it had been well established in the majority of the population and the risk/benefit ratio from its use is very low. And that risks can be identified and labeling provided for safe OTC use. Ironically, there's about eight areas B pregnancy, hypersensitivity, the GI, and so forth B but they felt that these could be handled through proper warnings and labeling.

The dosing schedule provided there is identical to that for acetaminophen that I discussed yesterday. And again, I must remind you, that the data that the Panel reviewed was the data of the 1960s and early 1970s.

The aspirin discussion is very extensive,

as I said. The Panel, in the case of the GI, concluded that aspirin has several adverse effects on the GI tract, ranging from relatively mild to severe. Mild gastric distress, superficial mucosal irritation and minor occult bleeding, serious mucosal erosion, ulceration or life-threatening, massive GI bleeding is discussed. They did say that massive bleeding is relatively rare and unpredictable.

The Panel also said that there is irritation or exasperation of stomach ulcers, stomach irritation and intestinal inflammation, which can occur in a significant number of individuals that take aspirin. And in their opinion, individuals with a history of symptoms of GI bleeding were especially at risk.

The report included a separate section on its interaction with alcohol, and the report included and cited studies demonstrating a synergism between alcohol and aspirin's ability to cause GI bleeding. Aspirin may potentiate bleeding from GI lesions even though aspirin alone may not initiate the lesion. But the Panel found insufficient evidence to include an alcohol warning in their recommendations.

The warning that they did propose in 1977 was: "Caution: Do not take this product if you have stomach distress, ulcers or bleeding problems except

under the advice and supervision of a physician." And they say this should equally apply to all other salicylates in the review B the carb-aspirin and the other non-aspirin salicylates, choline salicylate, magnesium salicylate and sodium salicylate, which were heavily marketed in the early `70s and were part of the review.

Now, keep in mind that at this time, when this Panel report was published, the only warnings that were required in the labeling of an aspirin product was the warning not to use for more than ten days and so forth and to keep out of reach of children.

Now the Panel also reviewed the effects of aspirin on the kidney and they found that although prolonged use of high doses of aspirin may produce kidney disease in some individuals, the risk is insignificant in the recommended target population, that is, namely, consumers using aspirin for general OTC use, and that a warning regarding aspirin causing kidney disease is unwarranted for OTC use.

The Panel also reviewed subjects with renal disease and there's an extensive discussion in the report. The evidence suggests that aspirin may contribute to an exasperation of chronic or acute renal disease other than analgesic kidney disease. It

is not clear whether aspirin contributes to renal deterioration in individuals with analgesic kidney disease and, again, the warning, they felt, was premature as definitive studies were lacking. So the report contained no renal warnings for aspirin, but a general GI warning among others.

In the tentative final publication, that is of 1988, the Agency proposed the dosing schedule that appears here, broadening it again for aspirin to include a five hundred milligram every three hours and one thousand milligrams every six hours. And it still limited the daily dose to four grams a day.

Now we've received no comments on the Panel's GI warning, and there were no comments on a statement of alcohol in or out of any warnings. So the FDA concluded in that same report the following warning which was somewhat broadened, but similar to the Panel's: "Do not take this product if you have stomach problems -- heartburn, upset stomach, stomach pain B that persist or reoccur, or if you have ulcers or bleeding problems except under the advice and supervision of a physician."

Now this warning has not been finalized as yet; it's still a proposal, but some manufacturers haven't included it in their labeling.

Now I think a little timeline is in order

for some of you to help us understand where we are today. We have the Panel report published in 1977 with this GI recommendation. In 1984, as Dr. Ganley pointed out, ibuprofen was approved under the NDA procedures for OTC use and it did not also include any specific GI warning.

And then we have the 1988 tentative final monograph that I just described with this GI proposed warning. And in 1993 naproxen sodium was approved for OTC use, and that same year, in June, the Committee considered the alcohol warning for acetaminophen that we discussed yesterday. And in September, we were back to consider the alcohol warning for aspirin and the other NSAIDs and, I might add, in 1995 ketoprofen was approved for OTC use and it did have an alcohol warning.

Now the data reviewed by the Panel in September of that year B now we're looking at the aspirin-type products, NSAIDs B was epidemiological data of the risk of upper-GI bleeding associated with alcohol with aspirin, ibuprofen and naproxen sodium. They did not consider ketoprofen at that time.

The data on the added effects of these ingredients with alcohol, data on the alcohol's ability to potentiate aspirin-prolonged bleeding times and data on the effects of aspirin, on ethanol

pharmacokinetics, and they also included the Panel's findings.

Questions asked of the September 1993 meeting were: Are the data sufficient to support an alcohol warning for those ingredients? And what type of information should an alcohol warning include? And should it be organ-specific? And what information should appear in labeling of combination products that contain both aspirin and acetaminophen?

The Panel concluded that these ingredients increase the risk of upper GI bleeding in heavy alcohol users or abusers and a warning is warranted. However, in this case, there was no consensus on an organ-specific warning. And just a few months earlier for the acetaminophen, there was a consensus to have the liver damage warning. And they also concluded that there was no data to support a warning for non-aspirin salicylates. And they felt that there was no need to specify a level of alcohol consumption in the labeling.

The FDA concluded in the 1997 proposed rule that we discussed yesterday that the history of heavy alcohol use or abuse may increase the risk of adverse GI effects, including serious GI bleeding and a warning is needed also for aspirin and the NSAIDs. And that specific warnings are more effective and

should include organ-specific information. Products with no warnings may lead consumers to conclude that they are safer for use with alcohol.

Therefore, the non-aspirin salicylates, the choline salicylates and so forth, should also bear an alcohol warning, because they have a similar safety profile and, without that warning, it would be implied that they were safer for use.

Now these conclusions were included in that 1997 proposal. Again, the comments were mixed and the Agency ended up with this alcohol rule. And the final rule has a labeling, alcohol warning: If you consume three or more alcoholic drinks every day, ask your doctor whether you should take aspirin, or whatever the NSAID is, or other pain relievers, fever reducers, because aspirin may cause stomach bleeding.

Now all OTC products containing these ingredients are required to include this warning whether marketed under the monograph system or under an NDA. And I think it's worth point out, as Dr. Jenkins mentioned yesterday, this warning is not telling you that you cannot use it; it's telling you to seek advice of a doctor before using. And it doesn't say "alcoholic warning." It's an alcohol warning; it doesn't specifically relate to somebody that might be an alcoholic.

It was hard to deal with this warning because if you had no number of drinks, then it would imply, you know, any alcohol, and we know people use it, wine, for the heart and so forth.

Now in 1998, we also published professional labeling that Dr. Ganley pointed to this morning. Now this is labeling intended for health professionals. It does not appear in OTC labeling, but obviously it's publicly available. You can look in the Code of Federal Regulations and you can find it.

In essence, it's a codified package insert for low-dose aspirin. And it contains numerous sections including sections dealing with warnings to the GI and warnings to the renal. And what I've done is just highlight some of these things in terms of the layman. It isn't professional labeling, doesn't necessarily occur in OTC labeling. And we also had adverse reactions that have been reported in the literature listed, and there's a whole, whole, extensive review and I'm sure many of you have seen that.

And lastly, as Dr. Ganley pointed out, in August we proposed to include ibuprofen in the monograph system. It's been used since 1984 and we felt that these terms and such could be, should be

included in its particular labeling. And what's important to note here that there are new terms that haven't appeared in OTC labeling, at least that I'm not aware of, for these products, like high blood pressure, heart or kidney disease, taking a diuretic or using over 65 years of age.

So today we have aspirin and NSAIDs which include that alcohol warning. We have NDA products that contain some stomach warnings; they're not consistent at the moment. And we have aspirin and other monograph ingredients that are not required but do, in some cases, include the 1988 tentative final proposed warning.

Thank you.

DR. CANTILENA: Okay. Thank you Dr. Gilbertson, Dr. Ganley. We'll now move directly to the open public hearing, public presentations. Rebecca Burkholder, the National Consumers League will be out first speaker. All speakers are reminded there is a time limit that was agreed to and for the first two speakers, they each have five minutes.

DR. BURKHOLDER: Good morning.

The National Consumers League, America's oldest consumer advocacy organization, is pleased to testify today about the potential of gastrointestinal bleeding with the use of non-prescription, non-

steroidal, anti-inflammatory drugs, or NSAIDs.

I would like to inform the Committee at this time 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 dinners and conferences. This amounts to less than one-half of one percent of our annual operating budget. NCL did not receive any financial incentive to appear at this meeting this morning.

Recent studies have recognized that the use of non-prescription NSAIDs increases the risk of gastrointestinal, or GI, bleeding by as much as two to three times. Overall, GI bleeding caused by NSAID use is now recognized as the most common, serious adverse drug reaction in the United States, and accounts for as many as 16,000 deaths a year.

If the FDA determines that the data and studies support the conclusion that consumers are at an increased risk of adverse GI events when using a non-prescription NSAID, then the labeling on these products should contain a clear warning to consumers of this risk and the packaging should include consumer education on GI bleeding.

Consumers today are taking a more active

role in their health care including self-diagnosing and self-medicating. Because of this trend to self-medicate, it is important that over-the-counter, or OTC, medications that pose a significant risk to consumers have a specific, clear warning about the risk on the label and that consumer education include details of the potential adverse events.

According to surveys conducted on consumer use and attitudes about OTC medications, consumers need more education on the proper use of all OTCs. A survey, commissioned by the National Consumers League, found that one-third of consumers do not regularly read the labels of OTC products before purchasing or using them. 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.

A recent survey by the National Council for Patient Information Education, NCPIE, a patient advocacy group, found that while 95 percent of consumers read some portion of the label, they do so selectively. When buying an OTC product for the first time, only a third look for the active ingredient and one in five seek out warning information. Over a third

of the consumers combined non-prescription medications when they have multiple symptoms.

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

What is clear from these surveys is that consumers need to be better informed about using OTC products. Labels, including warnings, need to be in easy-to-understand language and the involvement of health professionals could increase consumer understanding of OTC medications.

If the FDA finds that the increased risk of adverse GI events with the use of OTC NSAIDs is such that consumers should be warned, there are several things that NCL would like to see on the NSAID label.

First, an organ-specific warning that use of NSAIDs may cause stomach bleeding. This should be separate from the alcohol warning statement on stomach bleeding since that warning is directed at consumers who drink some alcohol.

Two, more specific information to consumers on the factors associated with increased risk of GI-adverse events, including a high daily

NSAID dosage and past history of GI problems.

Third, a consumer information leaflet should be included in the OTC NSAID packaging, explaining GI bleeding and listing the specific symptoms of GI bleeding, including black or bloody stools, severe stomach pain, vomiting of blood or vomit that looks like coffee grounds. Consumers should be advised to consult their doctor immediately if they experience these symptoms as they may indicate a more serious condition.

In addition to changes in labeling and packaging, an education campaign should focus on proper use of OTC NSAIDs, including proper dosage and the risk of combining OTC NSAIDs. This is especially important because studies have found that the risk of GI bleeding increases as the daily dose of the NSAID increases.

The campaign should encourage consumers to talk with their doctor, or other health professional, about any questions on taking OTC NSAIDs. Educating health care professionals, including doctors and pharmacists, on the risks consumers may experience with OTC NSAID use and how to best explain these risks to consumers should also be part of the campaign.

While NCL recognizes that non-prescription NSAIDs are an important part of a consumer's ability

to self-treat for headaches, muscular aches and the minor pain of arthritis, there also needs to be appropriate information on the risk of NSAIDs in order for these products to be used safely and effectively.

Thank you.

DR. CANTILENA: Thank you. Dr. Jolly, from Virginia. Is Dr. Jolly here? Okay, then we'll move right to the FDA presentations. These presentations will, have been allocated one hour and will be given by Drs. Weaver, our Dr. Cryer, Dr. Pelayo, and Dr. Griffin. Dr. Weaver.

DR. WEAVER: Good morning.

Today I'll be describing cases reported to the FDA's adverse event reporting system of gastrointestinal bleeding in individuals who ingested an over-the-counter, non-steroidal, anti-inflammatory drug or aspirin.

The non-steroidal, anti-inflammatory drugs have over-the-counter indications for use as analgesic and anti-pyretic. Aspirin has over-the-counter indication for use as an analgesic.

The adverse event reporting system, AERS, is an FDA database of spontaneously-reported adverse drug events. We searched AERS for recent U.S. cases of gastrointestinal bleeding attributed to the ingestion of non-steroidal, anti-inflammatory drugs or

aspirin. And we searched for these cases that were received by the Agency for the years 1998 through 2001.

We screened the cases for OTCness. For the non-steroidal, anti-inflammatory drugs, we did the screening at the time we did the review. We screened the cases for the use of an over-the-counter product, or for mention of over-the-counter use in the narrative of the report.

For the aspirin review, we originally reviewed all cases of gastrointestinal bleeding reported to the Agency in this time frame and that review is provided to you in the background material.

Most of the cases of gastrointestinal bleeding that were reported to the Agency involved the use of aspirin for vascular indications. For this presentation, I'm presenting only the cases in which aspirin was used for its analgesic indication.

Two hundred and seventy-nine cases are included in the two series. One hundred and ninety-seven case for the non-steroidal, anti-inflammatory drugs, ibuprofen, ketoprofen and naproxen, and 82 cases are for aspirin.

Our findings for the non-steroidal, anti-inflammatory drug series and the aspirin series were similar in most respects. Where the findings were

similar, I'm combining the information and I will also show you some differences that we found.

Most of the cases in the database were reported to us by health care practitioners. One hundred and twenty-five of the cases were reported by health care practitioners; we also received a fair number from consumers. We had 63 from, directly from consumers.

The mean age in the case series was 59 years. There was a wide range in this age. For gender, half of the patients in this series were male; 43 percent were female. And in the remainder of the cases gender was not reported.

When the indication for use of the product was included in the report, pains and aches and pains were most often reported. The next most commonly stated indication was arthritis, and this is osteoarthritis and unspecified arthritis. The next most commonly reported was headache, then back, neck or shoulder pain, then lower extremity pain and then fever.

When the location of the bleed was stated in the report, the stomach was most often cited. Next most commonly reported was the duodenum, then unspecified, upper-gastrointestinal site, then esophagus, then a lower GI site.

For the non-steroidal, anti-inflammatory drugs, the median time to onset from the time the patient first starting using the drug to the time the bleeding occurred was seven days. In the aspirin series, it was about a month, instead of about a week. But in both of those series, there was a wide range in time to onset.

We looked for risk factors in the cases and we used the risk factors that are published in the medical literature. We looked for previous gastrointestinal bleed or history of an ulcer or for helicobactor pylori. We looked for serious systemic disease. We also looked at social history, ethanol consumption or tobacco use, and we looked at the use of, the concomitant use of medications that could increase the risk of bleeding: another non-steroidal anti-inflammatory drug, aspirin, an anticoagulant drug, corticosteroid.

For high dose we looked to see if the patients were using doses over the labeled over-the-counter dose and for advanced age, we used age 65 and older.

Seventy percent of the patients in our series had at least one risk factor; 40 percent had more than one risk factor and 29 percent had no risk factors apparent in the report. The most commonly

reported risk factor identified in the cases was the concomitant use of another medication that could put the patient at increased risk. In about one-half of the cases, the patient was using another drug that could increase risk, and another non-steroidal anti-inflammatory drug or aspirin was the most common concomitant medications.

About 40 percent of the patients were of advanced age. We had a history of a previous gastrointestinal bleed or also h. pylori in 18 percent of the cases. Ethanol use was reported in 12 percent and tobacco use was reported in 5 percent.

Almost 14 percent of the patients in the non-steroidal anti-inflammatory drug series were using doses over the labeled OTC dose and that's not counting the possibly concomitant medication; that's just the drug that it was reported for. In the aspirin series only one patient was, exceeded the OTC labeling.

Ultimately, most patients in the series had a good outcome. About three-quarters of the patients were hospitalized and most of those patients did recover. However, 13 patients in the series died.

Conclusions that we have from looking at this is that gastrointestinal bleeding occurs with the over-the-counter use of non-steroidal anti-

inflammatory drugs and aspirin and that most patients required hospitalization and then recovered.

In terms of risk factors, most, but not all, of the patients in the series had risk factors for gastrointestinal bleeding and concomitant medications, advanced age and a gastrointestinal history were often reported.

DR. CRYER: Let's see here. Here we go.

I've been asked to give an overview of this subject on the gastrointestinal risks of over-the-counter NSAIDs with the aim of bringing the entire group up to a common level of discussion while several of us know these issues very clearly. I'll make a few disclaimers first.

In looking through this literature, most of what we know about it is about the effects of the prescribed products and there are fewer evaluations on the risk of the over-the-counter agents, and those evaluations which do exist in the OTC arena, many have looked at OTC doses in patients who chronically receive NSAIDs and patients with chronic diseases. And whether or not those evaluations or those observations in chronic patients with chronic diseases relates to the OTC use with acute, intermittent doses in patients with relatively, who are relatively healthy is unclear.

But having given the limitations of the data set, I'll just give this introduction by listing the NSAIDs that are available both by prescription and as OTC products. As you can see they're listed in three categories, the non-salicylates, the non-aspirin NSAID salicylates and the Cox-2-specific inhibitors.

Comments specifically about the OTC. Amongst this group of 26, only four are available in the OTC fashion, as you know: aspirin, ibuprofen, ketoprofen and naproxen. A few consistent observations are that the OTC doses are usually half of the prescribed doses, and I think it's important to point out that all of the OTC NSAIDs that are available are non-selective Cox inhibitors. So to the extent that Cox-2-specific inhibition imparts gastrointestinal safety, that would not be expected to be an inherent component of the OTC products.

Now, looking at the actual risk of NSAIDs, they're generally divided into, as we've heard, into three categories: those attributable to the GI tract, those attributable to the kidney and the platelet. I'm going to focus on the GI tract. Drs. Pelayo and Griffin will speak a little later, in a few minutes, about the kidney effects and, we're not going to have a lot of discussion about platelet effects, but as it relates to gastrointestinal events, the platelet

effects manifestations in the GI tract are largely a conversion of asymptomatic endoscopic lesions to clinically relevant bleeding lesions.

But with respect to the GI tract, the ulcers are the ones, the events of greatest concern and with regard to epidemiologic observations of not exclusively NSAID-related ulcers, but peptic ulcers in general, there have been a, this demonstrates a few interesting phenomena, which only reported to the `90s, I would say these, several of these concepts have persisted to current date.

And that is that if you look at the hospitalizations for uncomplicated ulcerations for both gastric or duodenal, they've been declining over the last several years. This is probably related to the decreasing prevalence and the increase in eradication of the number one cause of ulcer disease, helicobactor pylori.

But despite the decreasing prevalence overall of uncomplicated ulceration, interestingly for both, for the incidence of the complicated ulcerations, specifically bleeding ulcers, has been consistent and for duodenal ulcers, as you can see, has increased.

I would like to make the case that this increasing incidence of bleeding ulcers that we've

been seeing over the last several years is probably related to the increasing exposure of the non-steroidal anti-inflammatory drugs, much of which has been OTC, and I'll have a few data which support that contention in a few slides.

What we see endoscopically, as gastroenterologists, is shown here, very characteristically, in these NSAID users. We see this constellation of hemorrhagic lesions, mixed with erosive injuries scattered throughout the stomach, but principally in the stomach. Fortunately, most of these lesions are asymptomatic and not particularly of much clinical concern as it relates to morbidity.

The greater concern with these agents is typically shown here, as an NSAID-related ulcer and with regard to how frequently these endoscopic ulcers occur, there've been, there's just been a litany of data that look at this and, more or less, gastric ulceration has been reported, at least with the non-selective agents, to occur somewhere in this range, and the duodenal ulcer somewhere in this range.

The consistent observation being that gastric ulceration associated with NSAIDs is much more common than the duodenal ulceration. But, again, the caveat is this is endoscopic, these are endoscopic ulcers, at prescribed doses, much of which is

asymptomatic. With the regard to the incidences of clinically relevant ulcerations, ulcers that present with bleeding, it's somewhere in this range, probably about two percent, but at least should be in the one to four percent range.

That's the data as it relates to the prescribed products. Now what about the risk of these agents? Pretty consistent. These are, there's a compilation of observations over several studies, but they all pretty consistently tell the same story. They're placing at very high risk for this, is a prior history of a bleed, concomitant anticoagulant use or corticosteroid use.

Pretty consistently there's also been this kind of step-wise increased risk associated with increasing age. And specific to this discussion, it's clear that the risk of this problem is associated with dose, and to the extent that the OTC products are generally lower doses, at least a half a dose or less, then the risk should be somewhere within the range seen in the low-dose experience.

In general, I would say that a relative risk of three is probably a consistent observation that is seen throughout the studies.

A couple of the, few of the concepts that I'd like to review are the specific risks of OTC

NSAIDs and I'd like to talk about them as it relates to the non-aspirin NSAIDs versus aspirin. I think conceptually and mechanistically, these, aspirin separates itself from the non-aspirin NSAID, and so I'd like to discuss them separately.

Specifically, interestingly, with regard to the prevalence of this problem, this was one of the studies that addressed the prevalence of NSAID use in GI bleeders. These were all patients who presented to the hospital, acutely 400 of them with GI bleeding and they were asked whether they were using prescription or OTC products or whether they were using non-aspirin NSAIDs or aspirin.

So if you look at the OTC usage in these GI bleeders, 42 percent of GI bleeding was associated with OTC NSAID use, much of which was aspirin. If you look at all forms of NSAID exposure in this experience, 58 percent of the patients, 58 percent of GI bleeders in this experience were taking some form of an NSAID.

Other more recent studies have suggested that up to 80 percent of GI bleeders will have been taking some form of an NSAID, providing support for the epidemiologic observations that I've reviewed with you a little bit earlier. And much of this is OTC and much of the OTC experience, as you can see, is low

doses of aspirin.

Another prevalence study is this observation from, it's a GI bleeding registry that came from the American College of Gastroenterology in which gastroenterologists, practicing gastroenterologists, submitted information documents about their patients who had GI bleeding versus patients who were endoscoped who did not have GI bleeding.

And within this report the prevalence of use of aspirin, ibuprofen, naproxen and acetaminophen was seen for either upper GI bleeding, lower GI bleeding, total GI bleeding, versus no GI bleeding. And, as you can see, patients overall with GI bleeding more frequently used aspirin, ibuprofen and naproxen, but not acetaminophen, when compared to control patients.

Now the two studies that I've just reviewed for you actually were prevalence studies, and didn't address the risk as it relates to looking at the overall population of OTC NSAID users, i.e., the denominator, and then trying to assess the risk within that population of exposed patients.

A couple, this question is addressed from case control studies and cohort studies and I'll share with you two case control studies which have addressed

this issue of risk with OTC. This correlates a low or medium dose with OTC use and, as you can see, in the low to medium prescribed dose range, this relative risk was about two-and-a-half.

Another consistent observation that you'll see throughout the studies is that the risk with a low to medium dose, or OTC doses, is probably about half that seen with the higher doses of NSAIDs. Again, the caveat being is that we're looking at a database, an observational experience with patients with chronic NSAID exposure, of patients with chronic diseases rather than acute, short-term or intermittent use in patients who are relatively healthy.

Another observation, again this, this actually is another analysis of the ACG bleeding registry data that I previously showed you which indicated that in the patients, and this was specifically rather than low-dose, prescribed NSAIDS, this was specifically OTC NSAIDs, again the relative risk looked like it was three.

Interestingly, this because an outlyer the risk with the prescribed NSAIDs was lower than what we would have expected it to be, based upon our previous descriptions, and, amongst the OTC products, the risks of aspirin are higher than that of ibuprofen and the relative risk associated with acetaminophen was not

increased over controls.

Now within the ibuprofen group, OTC ibuprofen group, it's interesting; there is a dose-response relationship or at least in this bleeding registry experience there was a dose-response relationship that was observed such that as one went from doses of ibuprofen less than 600 milligrams per day up to the OTC dosage, you would see, develop the odds ratio increasing from 1.8 to 3.9 in this experience.

There hasn't been a lot, in my assessment, about the risk associated with the duration of OTC NSAID usage patterns. And this is, these are some data that come from a paper presented at gastroenterology meetings last year. You have OTC NSAID users, about 500 of them, and compared this to about a thousand controls who were not using NSAIDs.

With regard to how commonly or how frequently, or the duration of NSAID use, over the previous month, very surprisingly, 80 percent of the patients were using their NSAIDs for greater than 75 percent of the preceding month. Now in defense, however, of these NSAID users, much of this was probably daily use of low-dose aspirin. As you can see, 40 percent of the patients were taking their NSAID for prevention of cardiac problems.

Now having said that, this still leaves about another 40 percent of these chronic users who were taking it for other reasons, such as aches, pains, arthritis, headaches, suggesting that use of non-aspirin NSAIDs was also fairly prevalent and for durations longer than suggested or recommended by the label.

With regard to the GI risk that was seen with OTC aspirin usage in this survey, OTC users versus controls, the risk of having any GI problem over the preceding month was about 20 percent and, more pertinent to our discussion, the risk of having a GI bleed or an ulcer in this experience over the preceding month was about a 0.6 percent prevalence, which was a relative risk of two albeit with a lot of confidence intervals.

Associated with the use of these OTC NSAIDs was, very interestingly, the use of OTC GI medications which was much more commonly used in the OTC population than controls, probably for the control of the symptoms associated with their OTC NSAID use. The same committee, two months ago, recommended approval of OTC proton pump inhibitors. Most of this, well all of this was antacids or H2 blockers, but I would assume with the advent of OTC PPIs that they would also in the future be used for this indication.

That was the non-aspirin NSAIDs. What does the data say about low doses of aspirin? These are, this is one recent report of patients hospitalized for GI bleeding suggesting that aspirin at any dose was associated with the relative risk of about three, but that's across all doses of aspirin.

Looking more specifically at the dose-response relationship across the indicated doses of aspirin, in this placebo-controlled study evaluating low-dose aspirin for the prevention of TIAs over six years, there was an increase in rates of GI bleeding with aspirin 300 milligrams a day going to 1200 milligrams a day. This relative risk compared to placebo for 300 milligrams of aspirin was a relative risk of about 1.6.

Subsequent studies have looked at lower doses of aspirin than 300 milligrams a day, this being one of the studies that, again, another study that's looked at regular use of regular aspirin within this range of 325 milligrams a day or less, in the United States a relative risk of about two; in Sweden the relative risk was about 4. Looking at the lower, even lower doses of aspirin, this being another study, suggests that as one increases the dose from 75 to 150 to 300, odds ratios going from two to three to about four.

The mechanism of injury within the gastrointestinal tract, and this is well known to several in the room, there are several potential components. It's probably multi-factorial. But one of the components that's been most consistently accepted as a mechanism that underlies this problem is a reduction in prostaglandin synthesis, related to inhibition of the enzyme cyclo-oxygenase.

The studies with the Cox-2 specific inhibitors, I think, provide a pretty good proof of concept that if one does not inhibit cyclo-oxygenase or if one does not reduce prostaglandins within the stomach, one is not likely to see gastrointestinal, increased susceptibility for gastrointestinal ulceration.

So working with that concept of prostaglandin synthesis being a surrogate marker to suggest toxicity, we looked at that as it related to whether or not there was any dose of orally-administered aspirin which would be without gastrointestinal toxicity in a 90-day prospective study of, endoscopic study, of health subjects at baseline and then at 45 and 90 days.

Interestingly, aspirin at a dose of even 10 milligrams a day, given chronically for three months was associated with a 60 percent reduction in

gastric prostaglandins compared to baseline. In all of these doses ulceration, gastric ulceration was observed.

When answering the question of whether or not different formulations of aspirin would reduce the risk, this is one such study that suggests that the answer to that is `no.' If, irrespective of whether one gets enteric-coated aspirin, versus buffered aspirin, the risk for gastric or duodenal ulcer bleeding is not different from plain aspirin. There's been a subsequent experience from Denmark that also suggested that the preparation of enteric-coated aspirin does not reduce risk.

And then, so what do we do about this problem of the risk of gastrointestinal bleeding associated with aspirin? One recent report in the, a couple of months ago from the New England Journal of Medicine, suggested one proposal, and this was an evaluation of patients who were at high risk, meaning all the patients had had a previous history of ulcers which were healed and then they were given, in a prospective fashion, either aspirin at a dose of 100 milligrams or aspirin plus a proton pump inhibitor.

The points that I would like to make about this, one that I find very surprising, but if true is somewhat concerning, and that is that in this high-

risk patient population were given just aspirin 100 milligrams a day, that the incidence of recurrent bleeding was 15 percent in those aspirin users, reduced ten-fold to about one and a half percent with the use of a proton pump inhibitor.

What about this issue of aspirin in low, to what extent does low-dose aspirin increase the, change or modify the risk associated with non-aspirin NSAIDS. Two reports I'd like to review for you that might address that, this being the first. A national cohort study from Denmark looking at 27,000 patients given doses of aspirin within this range in which low-dose aspirin was associated with about a two and a half increase of risk over the general population, and combining it with aspirin, combining it with a non-selective NSAID, doubled that risk.

We get another piece of, another picture into this question from the class study in which celecoxib and the non-selective NSAIDS, ibuprofen and diclofenac B this being the six-month data, by the way B were looked at for the development of ulcer complications or symptomatic ulcers or ulcer complications. And, as you can see, in the patients not taking aspirin shown here, and the patients who were taking aspirin down here, that either for the non-selective NSAIDs, there was an increase in the

rate of the development of gastrointestinal bleeding of about two-fold, in those who were taking aspirin. And in the celecoxib, the increase ranged from about three- to five-fold.

So two pieces of evidence suggesting that somewhere in the range of two- to five-fold, aspirin, when given in combination with non-selective NSAIDs will increase the risk of bleeding above those patients who are not taking aspirin, just the non-selective NSAIDs or Cox-2 specific inhibitors alone.

What about, we've had a fair amount of discussion on ethanol this morning. Several studies that have looked at this. There've been, I will just say that it's, to me it's inconclusive but there have been several studies, several of which have supported a relationship.

Again, this is our GI bleeding database from the American College of Gastroenterology, suggesting an increased risk for this combination of alcohol plus an OTC NSAID when it's compared to either alone. I will say, one of the potential limitations of the studies that 12 percent of these patients had gastric or esophageal varices, suggesting a confounding relationship potentially of ethanol use leading to cirrhosis and an increased potential for bleeding when exposed to aspirin or a non-selective

OTC NSAID.

Another report looking at this association, comparing these various categories, but when looking across the various columns, comparing those who never drank to those who have taken ethanol, there was some increase in relative risk, albeit modest, comparing those who never drink to those who took ethanol, but with overlapping confidence intervals.

One of the questions that's been raised recently and was suggested yesterday in our discussion was whether or not acetaminophen has a risk for gastrointestinal injury. A couple of studies that have addressed this. One, which I think is clearly an outlyer, and one for which there has been a lot of discussion has been this study which suggested an increased relative risk for gastrointestinal bleeding associated with increasing doses of acetaminophen. This is clearly an outlyer study.

I think most gastroenterologists, if not all of us in the room, would suggest that acetaminophen is not associated with the risk for gastrointestinal bleeding. I think what we're looking at here is an instance of confounding by indication.

For example, several, when these authors adjusted their data for confounding associations,

specifically a previous risk, a previous history of gastrointestinal disease, these risks markedly decreased, suggesting that what we're actually looking at here is a reflection of risk of previous disease state rather than a risk associated with acetaminophen.

Another study looking at this is one which we've previously seen, I've showed you earlier, again showing that acetaminophen is not associated with the increased odds ratio of gastrointestinal bleeding at OTC doses.

Again, coming back to this argument of prostaglandins being intermediate markers to suggest the potential for ulceragenicity, we've looked at this question in a different way in a paper that we're going to present next month in our gastroenterology meetings. Again, looking at prostaglandin concentrations, and endoscopically-obtained biopsies from humans, with these various drugs, acetaminophen indeed when placed and evaluated in vitro, at various concentrations, has no reduction in gastrointestinal prostaglandins.

The superimposed white boxes are the expected serum concentrations that one might reach with clinically-relevant concentrations, or clinically-relevant doses of these agents. And you

can see, with acetaminophen, rofecoxib or celecoxib, no reduction, no significant reduction of gastrointestinal prostaglandins. However, with naproxen, at clinically relevant concentrations, almost 100 percent reduction in prostaglandins. We did not evaluate ibuprofen in this evaluation.

Since we looked at the question of how might acetaminophen affect gastrointestinal injury, I think it's also reasonable to ask the corollary of how are NSAIDs associated with hepatotoxicity. There has been a lot of data on this and, compared with other classes of drugs, hepatotoxicity with NSAIDs is really uncommon.

With respect to the sub-clinical observations of increases in liver tests, one percent with most NSAIDs, there is an outlyer, diclofenac, likely 15 percent increases in liver tests across the population. These are not clinically relevant in most instances.

One recent exception to that was a bromfenac, Duract, J which was introduced for clinical use in 1997, but removed in 1998 because of cases of hepatic failure. The mechanism of hepatotoxicity with NSAIDs in most instances is idiosyncratic, that is it's not related to dose, not related to duration. It's with the OTC NSAIDs; these are, as I said, rare,

also rare with aspirin, but there is some intrinsic hepatotoxicity associated with aspirin, appears to be related to dose. Less at 325 milligrams per day.

With respect to duration, if one is going to see it, it's typically with, during periods of time that are longer than six days at higher doses in patients with inflammatory conditions. One very clear example of this was Reye's Syndrome in which increasing doses in children with febrile illnesses was associated with significant hepatotoxicity, a disease which has been fortunately reduced and has led to recommendations for avoidance of aspirin in children with febrile illnesses, respiratory illnesses or vericella.

So, in summary, what, my assessment of this literature is that OTC NSAIDs are associated with some increase in GI risk. These GI risks of OTC NSAIDs include upper and lower gastrointestinal bleed. I didn't talk a lot about the lower GI bleeding, but there is an evolving literature to suggest that risk as well.

The risk appears to be related to dose. Much of the GI risk associated with OTC NSAIDs is related to aspirin, unfortunately, even at lower doses. Low-dose aspirin, combined with an NSAID, will increase that risk for bleeding above NSAID alone

about two- to four-fold. The enteric-coated or buffered aspirin preparations do not reduce the risk and hepatotoxicity with OTC NSAIDs and with aspirin are uncommon events.

So I'll turn it over to Dr. Pelayo, from the Division of Cardio-Renal Drugs.

DR. PELAYO: Good morning.

Mr. Chairman, members of the Advisory Committee, representatives of the pharmaceutical industry, FDA and guests, the purpose of the presentation is to review the potential for over-the-counter non-steroidal anti-inflammatory drugs to cause nephrotoxicity. The Division of Over-the-Counter Drug Products has asked the Division of Cardio-Renal to address the following questions: Are non-prescription doses of over-the-counter NSAIDs nephrotoxic and, if so, what is the outcome of a risk-benefit analysis?

Let us first review the recognized NSAID-induced nephrotoxicity. In the aggregate, clinical studies on the use of prescription doses of NSAIDs, reviewed by the FDA, have provided compelling evidence for sub-clinical, however less serious, renal toxic effects for these agents. NSAID-induced nephrotoxicity is characterized by fluid and electrolyte disturbances leading to sodium retention, edema and hyperkalemia. These drugs can also

adversely influence blood pressure control, causing blood pressure to increase.

An acute decline in renal function, which is associated with increases in serum creatinine could occur with the use of NSAIDS. And if severe renal ischemia develops, acute renal failure could result, proteinuria, nephritic syndrome, interstitial nephritis and varying degrees of renal impairment are uncommon but distinct NSAID-related nephrotoxicity.

Acute renal papillary necrosis is a rare form of NSAID nephropathy that represents a permanent form of renal parenchymal damage. Despite the well-recognized, acute biological effects of NSAIDs on the kidney, NSAID-induced, chronic renal failure as a result of chronic use is significantly less well-documented.

Albeit, the majority of healthy, normal subjects who are exposed to therapeutic doses of NSAIDs for a limited duration tolerated these drugs without untoward renal effects, a subset of individuals have been identified who are more susceptible to potentially life-threatening nephrotoxicity, including acute renal failure and serious fluid and electrolyte disorders. This at-risk population comprise subjects afflicted with volume depletion, underlying kidney disease, congestive heart

failure, liver dysfunction with ascites and the elderly.

Now, maternal use of NSAIDs in the last trimester of pregnancy has been associated with significant neonatal nephrotoxicity. The aforementioned renal-adverse events in at-risk populations which qualitatively define the safety profile of these drugs are currently described in the labeling for prescription doses of NSAIDS.

Next, the risk of nephrotoxicity needs to be quantified. So what are the rates of occurrence of NSAID-related kidney-adverse events for prescription doses? The point estimates a 95 percent confidence interval for these rates are not well-defined for either healthy or at-risk populations. Notwithstanding, the next five slides show representative incident rate for kidneyBadverse events identified in their review of the clinical database comprised of two clinical studies.

The clinical trials have prospective, randomized, placebo-control and parallel group design and a treatment duration of 18 weeks. Three hundred and sixty-five healthy subjects with osteoarthritis were evaluated per group. Incident rates for renal-adverse events, as reported by the principal investigators associated with ibuprofen, 200

milligrams, excuse me, 2,400 milligrams daily were compared to those documented in the placebo arm.

Only data obtained with the use of ibuprofen was represented. It should be noticed that there are not adequate data indicating significant difference in nephrotoxicity among NSAIDs. As can be seen in this slide, prescription doses of ibuprofen were associated with an incident of edema of approximately 4.5 percent, a value that was twice of that observed in the placebo group.

This slide summarizes the data on hyperkalemia. Hyperkalemia occurred at a rate of 0.8 percent with ibuprofen while no patient receiving placebo developed this adverse event.

This slide shows rates of occurrence for hypertension. Hypertension was reported in 5 percent of ibuprofen-treated patients and in 3 percent of the patients receiving placebo.

The incident rates for elevated serum creatinine are shown in this slide. This adverse event occurred with an incidence rate of 1.5 percent and 0.4 percent in ibuprofen and placebo-treated patients, respectively.

Depicted in this slide is the incident rate for proteinuria. Ibuprofen administration was associated with higher rates of proteinuria than

placebo, 1.1 percent versus 0.5 percent respectively.

The investigator reported for either group no cases of acute renal failure, interstitial nephritis, or acute papillary necrosis. This finding is not surprising since a significantly larger clinical database is needed to detect these renal-adverse events which are thought to occur at a rate of less than 0.1 percent.

Having reviewed the renal safety profile for prescription doses of NSAIDs, let us now focus on non-prescription doses of OTC NSAIDS.

Currently, there are three NSAIDS available as OTC drugs: ibuprofen was approved in 1984 with maximum daily dose of 1,200 milligrams, which represents approximately 40 percent of the prescription dose. Naproxen was approved in 1994 with maximum daily dose of 600 milligrams, which represents approximately 40 percent of the prescription dose. Finally, ketoprofen has been available as an OTC product in 1995 with an approved maximum daily dose of 75 milligrams, which approximately represents 25 percent of the prescription dose.

Of note, current labeling and packaging of these OTC NSAIDS do not have language concerning nephrotoxic risk.

Critical to the understanding of the

nephrotoxic risk, if any, associated with the use of non-prescription doses of NSAIDs would be to have safety data derived from clinical trials assessing dose level versus nephrotoxicity. Thus, ideally, assessment of the nephrotoxic risk associated with OTC NSAIDs should rely on data derived from prospective, randomized, placebo-controlled and adequately powered studies, comparing non- versus prescription doses of NSAIDs in healthy as well as at-risk populations. In this regard, it is the understanding of the Division of Cardio-Renal Drug Products that those data are not available.

Lack of ideal data to assess these nephrotoxic risks brings one to resort to significantly less adequate sources, for instance, retrospective, uncontrolled and underpowered studies, meta-analyses and case reports published in the medical literature.

In this regard, the National Kidney Foundation in 1995, convened a group of investigators and clinicians to consider and develop recommendations on the issue of analgesic-related kidney disease. To this end, the group of expert reviewers reviewed a database comprised of 556 articles published in the medical literature on aspirin, acetaminophen, aspirin-acetaminophen combinations and NSAID-related

nephrotoxicity.

Based on the totality of the findings supporting the notion that use of non-prescription doses of OTC NSAIDs carries a nephrotoxic risk, the National Kidney Foundation made the following recommendation: "There should be an explicit label warning patients taking over-the-counter NSAIDs of the potential renal risks of consuming the drugs."

Lastly, the assessment of the nephrotoxic risk associated with the use of OTC NSAIDs could rely on data collected by the adverse event reporting system. The Office of Drug Safety reviewed the archive of the adverse event reporting system for acute renal failure, chronic renal failure and renal failure cases reported following the OTC approval date for the three NSAID products when used in non-prescription doses. The cut-off date for research was August 10, 1999.

According to the reviewer, in each case, the best effort was made to retain cases in which it was known that either OTC dosages and/or an OTC NSAID product played a role in the drug reaction. Subjects with pre-existing conditions were not included.

The total number of adverse events reported was as follows: 13,141 for ibuprofen; 10,794 for naproxen; and 2,000 for ketoprofen, corresponding

to 15, five and four years of reporting, respectively. The reviewer identified 94 cases of renal failure for ibuprofen, 26 cases for naproxen and one case for ketoprofen.

Fifty-six subjects who used ibuprofen required hospitalization; nine cases needed dialysis and nine subjects died. Of note, 16 cases reported for ibuprofen were within the pediatric age group. Of concern, renal failure occurred within less than seven days of exposure to drug and in subjects without prescription factors.

For naproxen, 25 subjects were hospitalized. Four cases required dialysis and three subjects died. The only case reported for ketoprofen required hospitalization.

In conclusion, a risk-benefit analysis indicates that while the benefit obtained from the use of OTC NSAIDs only relates to the relief of symptoms, the use of OTC NSAIDs carries a nominal risk of nephrotoxicity. However, there are no data available to quantitatively define the risk. This lack of information prevents us from reaching a conclusion about whether the risk changes with dose.

Thank you for your attention.

DR. GRIFFIN: Good morning.

I was asked to talk about, we've had a lot

of experience doing studies on NSAID-adverse events in the Tennessee Medicaid database. We've been doing this for, well since Sid Wolfe from the public citizens group asked the FDA to withdraw peroxicam as an imminent health hazard. That was, I think, 1984 or '85. Some of you from FDA may remember that.

But a number of groups who were working with large prescription databases at that time were asked by FDA to look at their databases and sort of determine whether NSAIDs really did cause GI bleeding. And it's, you know, now that's pretty well accepted, but back in 1985 it wasn't.

So, we've done a number of studies with NSAIDs, using the Medicaid database and FDA has supported, at least in part, a lot of these investigations. So I'm just going to go through some of the lessons we've learned and share some of our experience with you.

So, first I'm going to talk about the GI complications and we have a little bit of information on renal complications from this database. This is actually information that Luis Garcia Rodriguez and others published from Saskatchewan, and I think it's really important because it really shows the epidemiology of serious ulcer disease and we're talking about ulcer hospitalizations and bleeding, and

it shows very nicely that the risk of these complications, the lower two lines represent people not on non-steroidal anti-inflammatory drugs.

As you can see, the risk increases with age, and because this is an arithmetic graph, you don't see so well what happens at the lower end of the age group. But the risk increases about ten-fold over the extremes of age. So age is a very important contributor to the risk of ulcer disease.

Now what NSAIDs do is they increase that risk about four-fold, or three- to five-fold, that depends on dose, and you can see that if you increase the, if you're at the higher age spectrum, when you increase that four-fold, you get up to pretty significant risks. We're looking here at absolute risks and you can see that in the older population, the absolute risks go from about four per thousand per year, four hospitalizations per thousand persons per year, to about 16 per thousand persons per year with non-steroidal anti-inflammatory drugs.

So what that means is that people who are using these drugs for a year at moderate doses have about a one to two percent chance of being hospitalized with a complication. Okay, so I'm going to try to help translate these relative risks into absolute risks where the data are there to do that,

because I think that's important when we're thinking about the risks to patients, that we really want to know what their absolute risk is.

Now, these are data from the Tennessee Medicaid database, and this is a big, computerized administrative database, and has very detailed information on prescription drug use and prescriptions filled. But I think there are lessons to be learned from these studies about over-the-counter drugs as well.

For these studies in both GI disease, people think of well, this is a big computer database and you're relying on ICD-9 diagnoses, et cetera, but for all these studies for the GI events and for the renal events, we went to the hospital, these are all hospitalized cases, we relied on ICD diagnoses to identify possible cases, but then we went to every hospital, we reviewed the records, we had specific criteria for what constituted an ulcer or, in the case of renal failure, what constituted acute renal failure. So these are real people with real diagnoses who had real events.

The comparison group are always a random sample, a stratified random sample, of other Medicaid enrollees who were not hospitalized. So they're a control group taken from the same population from

which these people who were hospitalized were from.

Okay, so I'm trying to concentrate on the NSAIDs that are available over-the-counter, so in our studies, this was done using data from 1984 to '86. People who used ibuprofen at doses lower than 2400 milligrams had about a doubling of risk of an ulcer hospitalization and the risk increased with increasing dose.

Similarly with naproxen at great than a thousand milligrams versus a thousand-plus, the risk increased with increasing dose. And for total NSAIDs, we were able to cut the dose levels a little bit less. So the lowest dose level is about, for ibuprofen would be like less than 1200 milligrams, but it's mixed in there with all the other doses. So, as you can see, when you combine all the NSAIDs, there's a clear dose-response effect and this has been shown in just about every study that has looked at it.

David Henry took a lot of these NSAID studies and did a meta-analysis, and there were actually five investigations at that time that included specific doses of ibuprofen and naproxen. People used different doses and in the ibuprofen low dose, most of the doses were around 1500 milligrams, the cutoff, and as you can see again, there's a higher risk with higher dose. But still with the low doses,

there's a 1.6, a 60 percent increase in risk of ulcer hospitalization. Similarly with naproxen.

Now, this is the absolute risk. These are, again, the data from Medicaid and it shows the absolute risks, the events per thousand NSAID users per dose. And again you can see that as the dose increases, the event rate increases. So we go from ten per thousand at the low dose to 15 per thousand at the higher dose up to 20 per thousand. Again, one to two percent of people on these doses are hospitalized per year.

Now all these people had a baseline risk of ulcer disease. So if you take out that baseline risk and you look at the risk that is just due to the NSAIDs, the events that would not have happened if people hadn't taken NSAIDs, that's what you see I the second set of bars. We're taking out the baseline risk of ulcer disease in the population and then you get between five and 15 per thousand events per year in this population.

We do have some information on risk by duration of use. So here I show you again in our population, people 65 years and older, the rate of non-users of hospitalization for ulcer disease was four per thousand per year. We see the greatest risk, the greatest absolute risk, in the first 30 days of

use, in our study. A lot of other people have reported similar things.

But really, in a group of chronic users of NSAIDs, the overall risk is driven by people who are using the NSAIDs for a long period of time. So that, for users of 31 to 180 days and users of greater than 180 days, basically the risk remains elevated. So most of the risk, this 16 per thousand or 15 per thousand, again, 1.5 per hundred, represent the risk of people who are long-term users.

The other important information is that people, the longer you take the drug, even though your risk drops a little bit after the first 30 days, you're accumulating risk. So if you're taking this for months at a time, you have a risk of one to two percent over one year; the next year, you have a, you continue to have a risk of one to two percent. So if you take these drugs for five or ten years, you end up with a substantial risk.

Okay. I'm going to talk about a few things that increase the risk of having an ulcer complication. We found that back in the 1980s, about one to three percent of people 65 and older were also getting a prescription for corticosteroids. I think that's probably higher now. And we found that if you were using an NSAID you were about as likely to be on

a corticosteroid as if you weren't.

Co-prescription, an NSAID plus a corticosteroid, increases your risk about 13- to 15-fold over non-users. So that the ulcer hospitalization rate in people who were using both of these drugs was about five to six per hundred people per year. So if you're using this combination for a year, your risk of a ulcer hospitalization was five to six per hundred.

Coumadin. Again, in our elderly population in the 1980s, about one to two percent of elderly were using coumadin. I think, again, it's probably higher now with the increased indication for use of coumadin, or anti-coagulation in the elderly. This increases the risk of GI bleeding about 12-fold over non-users, so that the hospitalization for GI bleeding among people who use both coumadin and NSAIDs is about three per hundred per year.

Now I'll talk for a minute about our study on NSAIDs and acute renal failure. We identified almost two thousand patients with community-acquired acute renal failure. The rate in our population was about four per thousand person-years. The median length of the hospital stay was eight days. Three percent of these people were dialyzed and the 30-day mortality was about 36 percent. Now this included all

cases of acute renal failure, so people who came in with sepsis and acute renal failure were included in the, a lot of these obviously were very sick people.

We found that people who came in with acute renal failure, about 18 percent of them were on NSAIDs. And NSAIDs were associated with an increase in risk, with an adjusted relative risk of 1.58. Other, there were a lot of other factors associated with acute renal failure: older age, male gender, black race, being in a nursing home, being on diuretics, taking ACE inhibitors and a lot of other co-morbidities. When controlling for all these factors, NSAIDs increased that risk. And obviously, if you have these factors plus using an NSAID, the risk is higher.

We tried to look at individual NSAIDs and for this outcome since it was more rare, it's hard to get very precise estimates of risk. Ibuprofen, we found, was associated with a risk of 1.63; naproxen we did not find a statistically significant increase in risk. Ketoprofen, 1.55, but the confidence intervals were wide.

We also tried to look at a dose response and the top bar indicates the upper 95 percent confidence intervals for these risks and again, we did see a dose-response effect with ibuprofen, so that

with increasing doses we saw an increase, a risk of acute renal failure. We also saw that the risk was greatest in the first 30 days of use.

Finally, I think that it's important to consider that over-the-counter drugs may be self-administered as previously prescribed. In other words, the doctor in the emergency room gave me 800 milligrams and therefore that's what I'm going to do when I go home with my ibuprofen. So I think although most of the studies that I've talked about and that you've heard about are not specifically with over-the-counter doses, people do take prescription doses even though they get the medicine not under a doctor's care.

Over-the-counter drugs may be used for long durations and, as you can see, if you're taking the drug for a long duration, even if the relative risk is only two instead of four, that risk accumulates over the time that you're taking it. Risk increases with combinations of greater than one NSAID.

We were pretty shocked in the 1980s when we found out that people using coumadin were just as likely to be using NSAIDs as not. There is no difference in NSAID use in coumadin users. So, and I think that that's probably not that much different today, unfortunately. People do not realize that

these drugs in combination with anti-coagulants are not good, and I think that the same probably goes for, you saw the multiple NSAIDs that are up there.

People don't realize that these are all one class, so they may be taking an NSAID from their orthopod and be given another NSAID by somebody else and be taking ibuprofen over the counter. So this is very relevant to OTC drug use. Even though alone, if the drug alone does not cause an effect, if added to another drug it causes an effect, it's still very important.

Again, for GI events, the risk increases with aspirin use, so a lot of people, increasing numbers of people are using low-dose aspirin.

Unfortunately, in our database, we're not, we can't study hypertension because we don't study things that you really need patients and to monitor them very closely, but I think, I feel very strongly that the data presented on hypertension need to be considered carefully, because small increases in mean blood pressure have large population effects.

People, to be anecdotal, most people realize that over-the-counter decongestants, they will call you and say "Oh, you told me to take this, but I have high blood pressure and the package says not to take it." But I never had anybody tell me they

couldn't take an NSAID because they have high blood pressure.

Other important effects of NSAIDs are small bowel and lower GI bleeding, dyspepsia, which increase health care costs and others that I won't go into, but I just thought as well as sharing with you some data, I took the opportunity to share some opinions as well.

DR. CANTILENA: Okay, thank you very much to all the FDA presenters.

We now have an opportunity for members of the Committee to address their questions to the FDA presenters, and we'll just open it up. Dr. Katz.

DR. KATZ: Dr. Cryer, why is it that older people have more ulcers from NSAIDs than younger people? What's the pathophysiology of that? Do we know?

DR. CRYER: Well, it's possibly multi-factorial. Certainly there's some physiologic basis and that's one area that we've specifically looked in. If you look at normal, healthy older individuals who are not exposed to an NSAID, there is an age-related decline in gastrointestinal prostaglandins which appears to just sequentially decline with decades, with advancing age.

For some, but not all NSAIDs, there also

appears that there may be some pharmacokinetic proportional changes with advancing age for some of them; as individuals have aged the serum concentrations with similar doses have increased when compared to younger individuals. There are other complications as well.

DR. CANTILENA: Dr. Clapp.

DR. CLAPP: My question is for Dr. Pelayo. With regards to the data that you found in the adverse event report about pediatric renal failure in association with ibuprofen, or NSAIDs, can you tell me specifically the circumstances of the renal failure for those 14 children? Was this dose-related? Was it relative to improper dosing or overdose due to the form of the ibuprofen, or, more information, please.

DR. PELAYO: I would like to ask Dr. Johnson to respond to your question. He is the reviewer of that particular data. But there are several cases reported in the literature. Actually, there is an article published by Dr. Mendoza from UCD, in which -- nine cases of acute renal failure. The acute renal failure was related to acute chronic cases, and in other cases to acute interstitial nephritis and there was no confounding disease. They were healthy individuals. There was only one case in which alcohol was related.

DR.CLAPP: One case?

DR. PELAYO: One case in which alcohol was part of the picture. That is to say, they take a drink, they dehydrate, they take an NSAID, an over-the-counter NSAID, and that doesn't seem to be a good combination because alcohol would lead to dehydration, and that's a very important factor for the development of acute renal failure. Dr. Johnson?

DR. JOHNSON: With regard to, I'm Mike Johnson; I'm from the Office of Drug Safety. With regard to the pediatric cases, this was ibuprofen or renal failure, pediatrics, I believe you asked about the dosage. One of the screening points on this was to remove anything that was not OTC dosing. So the overdoses, suicides, or things like that were all pulled out initially, so they weren't included here. The dosage on this, this is daily dosage now and this doesn't speak to the distribution of it throughout the day, the daily dosing on these cases amounted to a hundred milligrams B there were two of those B two hundred milligrams, there were two; four hundred milligrams, there were four; and six hundred milligrams, there were two. Okay, and that's the dose distribution; the others were unknown.

Any other specifics on that? In the pediatrics. I'm sorry if I missed it.

DR. CLAPP: My question also, the absolute dosages, but was that the appropriate dose per kilogram for these children because of the difference in a 10-kilo taking six hundred milligrams is certainly a problem, but six hundred for a 40-kilo child is not an issue.

DR. JOHNSON: Right. You know what, I don't know. I'm sorry. I'd have to pull it out.

DR. CANTILENA: Dr. Brass, then Dr. Laine, then Dr. Cryer.

DR. BRASS: I'd like to first follow up Dr. Katz's question with Dr. Cryer. I was also under the impression that there's difference not only in the mucosal injury but, in fact, a major factor in the elderly and in some of the situations like corticosteroids was the differential presentation, that the patient would simply present with more severe manifestations for a given level of injury because of failure to recognize early warning, the lower prevalence of early warning signs in the elderly, et cetera, leading to a more severe presentation, showing up at hospitalization databases, GI bleed databases, etc. Could you comment on that? And then, the second questions, related to that is, with the issue in the elderly, are there any data about the pharmacodynamics for efficacy in the elderly? That is, do the elderly

require the same plasma concentrations to get a beneficial effect of these agents as the young?

DR. CRYER: I'll comment on the second question first because that's the one that I clearly don't know the answer to since I don't concentrate on efficacy. So maybe someone else can more expertly comment about changes in efficacy with analgesics, or specifically NSAIDs, with age.

With regard to presentation, you're absolutely right. I think, in fact, Dr. Griffin has actually, if I'm not mistaken, but certainly other data bases have kind of given us this data that the elderly do tend to more frequently have a more common asymptomatic presentation, that is not having had preliminary symptoms prior to presenting with a catastrophic event such as a bleed. And the reason that the herald symptom of dyspepsia would be helpful is that those patients would more likely present for evaluation earlier on in the course of their ulceration prior to a bleed.

DR. LAINE: Can I just disagree with that a little because I, I'm not absolutely sure that's true because when you look at studies, we and others who look at endoscopic ulcers, age is also a significant risk factor just for endoscopic ulcers, and it's a similar increased risk factor for the

development of clinical events. So I'm not actually sure I agree with that, but I think there are data that once that person bleeds, then their mortality is far higher. So my own view is I'm not sure it's the presentation but the outcome once they present with that clinical complication.

DR CANTILENA: Dr. Laine.

DR. LAINE: I had a question for the FDA and it may not, none of you here may be able to answer it, but I was actually struck by the alcohol warning in the NSAID label. As someone's who's interested in this, I have actually never been, really been a believer that there's clear evidence that alcohol potentiates the risk of bleeding in NSAID or aspirin users.

Certainly, if you're, if you already have varices it may be a problem, and, as we've heard, if you already have cirrhosis, NSAIDs are quite bad from the renal point of view. But as we saw today from Byron's talk, that may have been, there may have been an additive effect of alcohol and NSAIDs, but most of the studies I'm aware of, both database studies and prospective trials, don't really clearly show alcohol as a risk factor. They do show these other things we've talked about, age, bleeding, et cetera. So I was wondering if you have other data to share with us

that can show me why you did that, or was that just to even the playing field when you did the acetaminophen label?

DR. CRYER: I would ask the same question.

DR. GANLEY: I'll let one of the historians here give that answer.

DR. LUMPKINS: Yes, basically the Agency's argument in the final rule was the additive effects, the ill effects of alcohol in addition to the ill effects of the NSAIDS.

DR. LAINE: It just strikes me as, then we were just saying that alcohol is bad so don't drink, but I'm not sure that, how it relates to the fact that NSAIDs may be bad, alcohol may be bad, they're both bad, but I don't understand, it seems to me that when we put it in the label, it's indicating a potentiation somehow, such age potentiates other things.

DR. LUMPKINS: There's no data of any potentiation.

DR. LAINE: Okay.

DR. LUMPKINS: The theory was two bad things together aren't going to make a better thing.

DR. LAINE: Well, you can say that about lots of things, anyway, okay, I mean, I just B later, we might consider revisiting that.

DR. CRYER: Well, I also have the same

questions, Loren, as it related to the gastrointestinal risk of the combination of alcohol and NSAIDS. But one of the things that caught my attention earlier on in Dr. Gilbertson's presentation was that, possibly part of that discussion, decision, was made upon the interaction at areas outside of the gastrointestinal tract, for example, potentially the increase in bleeding risk or the increase in drug-drug-alcohol-aspirin interactions.

DR. CANTILENA: Yes, actually, that was a part of it. I was actually here in 1993 on that committee, so that was indeed part of the information that we had in front of us.

We have Dr. Davidoff and then Dr. Katz.

DR. DAVIDOFF: Yes, I had a question for Dr. Pelayo, regarding the statement that he put up about, from the National Kidney Foundation, which talks about, recommends that there be an explicit label warning, warning patients taking over-the-counter NSAIDs of the potential renal risks of consuming the drugs. My question is whether your understanding is that that statement includes acetaminophen or not.

DR. PELAYO: No, that wasn't specifically related to the use of NSAIDs.

DR. DAVIDOFF: Well, I've raised the

general question, then, about acetaminophen because even though today's discussion is not about that drug, as I recall, the initial concern about the chronic use of pain relievers really began with phenacetine which, I understand, is effectively acetaminophen. And whether, if we're going to be talking about at least chronic renal failure in connection with the NSAIDs and aspirin whether we need in some fashion, maybe not today but however, to revisit that question in connection with the labeling of acetaminophen.

DR. CRYER: Okay, we can actually chat about that later. We have Katz, Cush and Rumack.

DR. KATZ: Comment and a question.

First, to me, I'm not sure I understand the relevance of the additive versus synergistic distinction as far as what consumers need to know. If there's an additive effect, to me that seems relevant as well as much as a synergistic effect would be. And my question is for Dr. Griffin, if she's still around, oh, hi. Do you have data on the relative risk of GI bleeding or GI events in patients on a combination of coumadin and Cox-2 inhibitors? And how that compares to NSAIDs?

DR. GRIFFIN: Not yet.

DR. CANTILENA: Dr. Cush.

DR. CUSH: I have two questions, one for

Byron and one for Dr. Ganley.

Byron, in your GI Advisory Committee and the approval, or tentative approval of OTC PPIs, was it ever discussed about the combined use of that with these aspirin-like drugs?

DR. CRYER: One slight correction, that was actually this committee, a couple of months ago, and I do not believe that was part of our discussion as I remember it, but many of you may correct me on that.

DR. CANTILENA: Okay. No, I don't think it was either. Dr. Ganley.

DR. CUSH: Dr. Ganley, could you clarify something for me about the two pathways for OTC drugs you discussed both yesterday and today, but today it becomes a little more germane, one being the drug monograph and the second being the new drug application. It seemed to me the drug monograph was sort of a historical grandfathering-in of historic drugs, such as acetaminophen and aspirin. And then the NDA was for new prescription drugs that then went on the market as OTCs. But then you mentioned that there's going to be a monograph now on ibuprofen. So how does that --?

DR. GANLEY: Yes, what happened is that a manufacturer submitted a citizen's petition to the

Agency requesting that ibuprofen be amended to the monograph for internal analgesics. And they can do that, and it's sort of a time and extent. After the regulation's printed, and after five years of marketing, where we have some historical perspective on the OTC marketing of a product, under an NDA, you can submit a citizen's petition to have it put into the monograph. And that's what was done here.

And so, several years ago, the manufacturer submitted the petition, sent in supporting safety data and thus the proposal rule, or proposed amendment to that monograph. And so that proposed rule is now out for comment and people can say, yes we agree with it, no we don't agree with it, or whatever. What it does change then, is that companies would no longer have to market under an NDA and they can market under the monograph, which relieves them of some of the regulatory burdens of, you know, providing information to the Agency before they do that. As long as they follow the conditions of use under the monograph. Did you understand that?

DR. CANTILENA: Okay, we have Rumack, Alfano, then Cryer.

DR. RUMACK: I'd like to make one quick comment on the question about phenacetine and acetaminophen. Acetaminophen is a metabolite of

phenacetine, but there is no back metabolism, except in some animals. And the phenacetine that produces the renal problem is a metabolite called paraphenatidine. So, all that you can see in animals, acetaminophen back-metabolizing to phenacetine, producing renal problems, you do not see that from acetaminophen.

I have a question for Dr. Weaver. We've heard from Dr. Griffin that many patients take the over-the-counter dosage of the NSAIDs at prescription levels, and we heard from the National Consumer League that about a third of them, of their patients take greater than the over-the-counter dose. The data that you presented to us was just the over-the-counter products and I wonder of the AERS database has been looked at for the higher the prescription level that would answer the question raised by Dr. Griffin and the National Consumer League.

DR. WEAVER: We did, when we looked at the non-steroidal anti-inflammatory drugs, we looked at the over-the-counter use, not specifically at over-the-counter dosing and we did find that 14 percent of the patients in the, using non-steroidal over-the-counter drugs, were using it at over the OTC labeling.

DR. CANTILENA: Okay, Dr. Alfano, then Cryer, then Kopp.

DR. ALFANO: This is a question, maybe, for Dr. Griffin, maybe Dr. Pelayo, and maybe some of the statisticians on the panel can help me with this. Because I'm trying to understand, and when you spoke about relative risk of drug A versus drug B. And as I look at that, and we talked a little bit about this yesterday, we're doing that without any denominators in terms of who's out there and how many people are taking these drugs in the population that doesn't present with such a side effect.

So I guess my concern is, or my question is, are we really talking about a relative risk or a probability that someone will appear in your database, versus a relative risk to the population at large? It sounds to me, you know, has the ring of relative risk to the population at large, but since you don't know the denominator, I don't know how you can calculate that.

DR. GRIFFIN: In our study we know the denominators. We have a population and we know everyone who's using an NSAID. So, we can look at people who use an NSAID and look at their absolute risk of being, and I tried to show you the absolute rates of ulcer disease in people using NSAIDs versus those who don't.

So if we took a thousand NSAID users in

our population and they used the drug for a whole year, then we would find 16 were hospitalized for an ulcer complication. And we took a thousand people from the same population who weren't using NSAIDs, four of them B these are the averages B four of them would be hospitalized for an ulcer complication.

Okay, so those are absolute rates; that's, I think, what you're trying to get at.

The relative risk is derived by putting one rate over the other, the rate of those exposed B the 16 per thousand B divided by the four per thousand. And that gives you the relative risk of four.

So, when you're talking about a relative risk, you're always, what you don't know, and I think what's confusing is what we don't know is, well, what's the baseline rate? If you know what the baseline rate in your population is, then you just multiply it by the relative risk. So if your baseline rate of ulcer disease is one percent and you have a relative risk of four, then you're increasing it up to four percent. Does that make sense?

DR. D'AGOSTINO: In your presentation, you occasionally, if I heard you correctly, said the relative risk was somehow rather more important where, in some sense, the absolute risk because you do have

the base and, possibly, I don't know if some of you, the confusion, but they were constantly, you were constantly presenting absolute risk which I presume you got from your database and then went to relative risk. So, that's all, was there someone else who was presenting it, you had a question on the, that you had a question on the relative risk being produced?

DR. ALFANO: No, it's just the databases that, the AERS for example, where you don't have how many people are taking it.

DR. D'AGOSTINO: Were they, I don't recall them presenting relative risk at that point.

DR. CANTILENA: Okay, Dr. Cryer, then Dr. Kopp.

DR. CRYER: Okay, so, my question is actually for Dr. Griffin.

One of the things that struck me from your presentation was your report on the risk of, in intermittent users of NSAIDs from your Medicaid database experience. And I would think that the intermittent users who, I think, were about at a three-fold increased risk compared to non-users, might parallel what one might expect to see in the OTC-using population. So the question is, is, I'm assuming that the intermittent use was across all doses of prescribed NSAIDs, and whether, the question is

whether you specifically teased out the low-dose use within that intermittent group.

DR. GRIFFIN: No, we didn't. I mean, that intermittent and chronic users were about four-fold, actually, above, they were 15 per thousand and 16 per thousand, about four-fold higher. And basically, if you were filling your prescription every month, we called you a chronic user. And if you skipped a couple months in between, and only filled it part of the time, and you know, didn't fill it religiously every month, we classified you as an intermittent user. And they had really similar risks.

DR. D'AGOSTINO: My understanding from your presentation is that it had to all come from prescriptions. I mean you don't know anything about NSAID use over the counter. Am I correct?

DR. GRIFFIN: Well, we know about NSAID use over the counter only from the medical record and we know that about five percent of people who we recorded as non-users were actually using OTC NSAIDs, or using NSAIDs, according to the chart. So there's obviously some misclassification when you look at a filled prescription; not everybody is actually taking the drug every day. And if somebody didn't fill a prescription, they could still be taking their spouse's or their friend's drug, or buying it over the

counter if they choose to buy it rather than get it free from Medicaid.

But I think our data, and we have some interview data as well, indicate that the filled prescription is a pretty good surrogate for actual use, in this population.

DR. D'AGOSTINO: But as prescription. I mean they, if any of these bought over the counter, and so forth, you could get possibly that information from questioning,

DR. GRIFFIN: Right.

DR. D'AGOSTINO: But you have no sort of systematic way of knowing how to adjust for that.

DR. GRIFFIN: Right.

DR. CRYER: In follow up to that comment, I would like to remark that while you're, the limitations of looking at prescribed databases are acknowledged, I did, there are some, but fewer, data sets which looked, which look exclusively at OTC use and I reviewed several of those which you. And even in those with exclu-- with specific OTC use, there was the increased risk which was, interestingly, not too different from the low-dose use in the chronic, prescribed database series.

DR. D'AGOSTINO: No problem with that, just in terms of how we should interpret the data that

was presented. Yours, data set, was obviously quite different than those. Thank you.

DR. CANTILENA: Okay, we have Dr. Kopp, Uden, Davidoff.

DR. KOPP: So, I have questions for Dr. Griffin and Dr. Pelayo.

To follow up on that last point, if a patient was not taking prescription non-steroidals, but was hospitalized with acute renal failure and gave a history of over-the-counter, would they be put into the non-steroidal user group?

DR. GRIFFIN: No. We tried to estimate what a missed classification was, but because we didn't have information on the controls, on non-cases, that we really couldn't, we didn't try to adjust our risk. But I think the result of this type of misclassification would be to underestimate risks.

DR. KOPP: Right. Yes, I think that's a good point. And just to follow up, you gave the adjusted relative risk of 1.58 for all non-steroidals for acute renal failure. What's the confidence interval, and specifically does it cross one?

DR. GRIFFIN: No. That was statistically insignificant. I don't have the B

DR. KOPP: Okay. Thank you. And then a question for Dr. Pelayo. You were careful not to get

into, let's see, where am I looking, to the very difficult area of the risk of non-steroidals in chronic renal failure. So chronic use of non-steroidals.

And I know why you did that; it's retrospective studies and they're flawed and they disagree with each other. But I also notice the same NKF report suggests that the prolonged, regular use of non-steroidals should be discouraged. If such use is necessary, renal function should be monitored periodically.

Now I realize we don't have much data, but do you think anything should be said on the label about issues of regular use of non-steroidals and the risks for chronic renal failure?

DR. PELAYO: Well, I think it all depends how much weight you put on the data available. I mean, if you do believe that the data unequivocally is telling you that, then you should include it. You want my personal opinion, Jeff?

DR. KOPP: Yes.

DR. PELAYO: I can, off the record B

DR. CANTILENA: Yes, how about if you hold on that? Because I think, you know, we'll probably be, you know, discussing that at about 2:30, roughly. Okay. Dr. Uden, Davidoff and Johnson.

DR. UDEN: My question is also for Dr. Griffin. In the data that you presented, you presented hospitalizations. I assume that not all people with ulcer complications will be hospitalized. Do you have any clue as to what percentage would be hospitalized versus not? Because that would then be clearly an under-representation of your risks.

DR. GRIFFIN: Right. I think in the 1980s, more people were hospitalized with these things than probably would be today. And we were focusing on events that we thought would result in a hospitalization. But, I mean, I think there's a whole series of dyspepsia requiring a procedure, that we really didn't look at in these studies.

We did do a cost analysis, and we found that the, what drives the excess cost, the sort of adverse event cost, if you're just counting not quality of life or anything like that, is really the excess in prescriptions for GI drugs, like H-2 blockers. Really drives the costs more than the hospitalizations do, because they're very common and they have, people on NSAIDs have about double the chances of being on an, well back then on an H-2 blocker; now on a PPI. So that causes a significant cost. So I guess it depends on what end point you think you want to focus on. I think the FDA has been

very interested in these serious adverse events.

DR. LAINE: Well, I have some data from prospective, 8,000-person outcome studies, and let's say with naproxen, about one and a half, well, over four percent of people had clinical events, but let's say one, not, just under one and a half had complicated events. But not all those were hospitalized, probably on the order of one percent. So, it's very rough, but if we can say two-thirds of people, three-quarters. So a number of people may have minor bleeding and, et cetera, that is significant but may not get hospitalized.

DR. GRIFFIN: Right. I think all of that is also depending on, you know, how many gastroenterologists there are, who's going to scope them. Because at any given point, 30 percent of people on NSAIDs are going to have ulcers if you scope them. Right.

DR. LAINE: Those were clinical outcome studies, not endoscopic studies.

DR. CANTILENA: Okay. Dr. Davidoff, Johnson, and then Dr. Wood, and then a break.

DR. DAVIDOFF: Yes. I have a question for Dr. Griffin that has to do with the risk over time because your data, as other people have shown, made it look as though, in some sense, the risk was greater in

the first 30 days and then dropped off. But my interpretation of that is that if you get a substantial complication in the first 30 days, you stop taking the drug. So, later on, you drop out of the population who's considered to have an event. Because you don't have any more events. Or the rate goes down. Or put another way, that if you had gone back to taking the drug, I think that's the important point, after you'd had an event in the first 30 days, you would in fact be at a continuing high risk, maybe even higher than the people who did continue.

So I guess my question is, do you think that that is a reasonable interpretation, and from that point of view, do you really think that the risk stays up with time or even perhaps increases with time, but you just can't see it in the real world?

DR. GRIFFIN: Well, I think, I think two things. One is that the number of events per people taking them are actually fairly small. So I'm not sure how much that influences the long-term risk.

The other thing is, unfortunately, people do start taking the drugs again, and enter into the population again. Surprising as it may seem, that people have GI events and then go back to taking these drugs. I don't know. Not everyone has shown that higher risk in the first month and it's, you know, I

don't know. Some people think it may be due, there may be some gastric adaptation. I think the important point is, although it looks pretty dramatic, this risk is only for a short period of time. And that what's driving the relative risk of four that we observe is this, the 16 per thousand that you see in long-term users. I think you're right, you know, maybe you're selecting out the people at highest risk, but I think that what's driving the big numbers are the chronic use at 16 per thousand.

DR. LAINE: Can I just comment too, we have prospective data that's being published later this year on that and others. The epidemiologic studies show that, but the prospective studies don't actually show that as long ago as John Carotta showing a stable increase.

We actually looked at this too, and over, beginning with 4,000 naproxen patients followed for up to 13 months, meaning at nine months there was a steady increase over time. It didn't change. Initially, we looked at base line versus no base line NSAID use, and what was fascinating, to me at least, was the no base line NSAID use was a significant risk factor for developing events. But the rate stayed the same over the nine months; it didn't decrease, which is against what, you know, we all thought, that early

on they would just have events and drop out. So it's interesting, but anyway the rate in the prospective experimental studies seems to stay the same over time.

DR. CRYER: Just to make one comment about this issue as well. I think the issue as I kind of see it as it relates to the time relationship of NSAID exposure, is whether or not this risk can occur within the period of time that OTC NSAID users are generally taking their medicines. And the data that caught my attention from Dr. Weaver's presentation, and I don't know if you want to comment on this, is that in her OTC evaluation, the median time to onset of one of these events in the NSAID users was seven days, which clearly spoke to the issue that yes, this is a short-term phenomenon and yes, this may, this should occur within the OTC users.

DR. LAINE: But don't you think, most of us I think in GI think that that's probably what was talked about B an exacerbation of a clinically silent lesion. In other words, we don't think that it made the lesion in seven days, but more likely, would you guys agree, that there was a clinically silent lesion there, let's say an h. pylori ulcer or something else, that then was made clinically manifest? That's my interpretation of these things.

DR. CRYER: Yes, I mean mechanistically I

would agree that's clearly plausible, and actually probable. But I think the most important issue there is actually the outcome and in fact, the fact it does occur within the first week.

DR. CANTILENA: Okay, Dr. Johnson, then Dr. Wood and then our break.

DR. JOHNSON: I have a question about a population that hasn't been really discussed in either before Dr. Griffin or Pelayo. And that is whether in your analyses you have looked at heart failure exacerbation. So patients who are stable on their heart failure regimen and then have exacerbation relative to NSAID use. I mean there's clearly data that look at patients admitted to hospitals and inappropriate drug use, and NSAIDs is sort of a big player in that, is an important contributor. And I wonder if you've looked at that population in any fashion?

DR. GRIFFIN: We haven't examined that in Medicaid. David Henry looked at that. Another group looked at, I think, a couple groups have reported about a doubling of risk of heart failure. In our, people that come in which renal failure are a mixed group of people. They're people that have sepsis, who have heart failure, or who have pneumonia primarily. Those are the people, elderly people, when they come

in with acute renal failure. So a lot of the people that we looked at in our renal failure study were coming in with both renal failure and heart failure. So certainly, I think, the data, those data are consistent. If you exacerbate hypertension, certainly, that has, and if you cause fluid accumulation, I think there are a lot of data to suggest that NSAIDs do, as well as a few studies that suggest that NSAIDs do increase the risk for heart failure.

DR. CANTILENA: Dr. Wood.

DR. WOOD: Marie, one of our jobs, I guess, this afternoon will be to decide on labeling changes that could reduce the risk for individuals. And one of the comments you made, as you know I've seen your data many times before, but it might have been missed by people, was the extraordinary increase in risk in patients who were taking corticosteroids and warfarin simultaneously. Were there any other risk factors that approached the 12-, 15-fold changes that you saw with corticosteroids and warfarin?

DR. GRIFFIN: Certainly people with a, we didn't look at the absolute rates, but, people who had a past history of a GI event, and Loren, you may have more data on these people with multiple risk factors, but people with a past history of a GI bleed have a

very high risk of, I think it would probably be up in that five percent range. And then when you get at the extremes of age, if you get very elderly people who have co-morbidities, some of the ARAMIS data, Jim Fries may want to comment on this, suggests that people with cardiovascular disease-- But when you start accumulating these risk factors and when you get up into people who are older, oftentimes they have multiple risk factors, and so all these things work together. So they may not only, they may be 70 and on corticosteroids and have had a GI bleed in the past, and then you get up a very substantial risk.

DR. CANTILENA: Okay, is that in follow-up, or-- ? Okay. Then if you wouldn't mind holding that until afterwards, why don't we take a 15-minute break. We'll be back at 10:25.

(The proceedings went off the record at 10:11 a.m.)

(10:27 a.m.)

DR. CANTILENA: Okay, while people are returning to their seats, I've just been asked to make one request, that you please turn your cell phones and, you know, pagers, into the silent mode please, so we don't hear your cell phones ringing and your pagers going off.

We're now going to have a 30-minute presentation from Bayer and the presentation will be

led by Dr. Heller who then will introduce his fellow speakers. The sponsor has 30 minutes total for the presentation. We will ask you to stay on time. We have to stay on time for the program, so we'll be on top of the clock today, as they say.

So let me have Dr. Heller, please, start for Bayer. Thank you.

DR. HELLER: Thank you.

Mr. Chairman, Members of the Committee, FDA, I'm Allen Heller, Vice President for R&D, Bayer Consumer Care. Bayer appreciates the opportunity to address the Committee this morning.

As you are aware, Bayer is a leader in the analgesic category with over 100 years of market experience. While we are best known for Bayer aspirin, Bayer markets a range of analgesic ingredients. Our focus today, of course, relates to aspirin and to naproxen.

I would like to briefly review Bayer's position with respect to questions posed today to the Committee. It's Bayer's view that each analgesic ingredient requires labeling that's appropriate for that ingredient. But also it requires labeling that's appropriate for use, appropriate for the pattern of use. Thus, it is inappropriate to apply in labeling the risks from chronic, long-term prescription dosing,

to apply those risks to short-term, OTC dosing.

Importantly, as stated by FDA, and as we will show you this morning, all of the OTC analgesic ingredients are safe and effective and, when used according to label, there are no meaningful overall safety differences between them. For the analgesics under discussion today, aspirin and the NSAIDs, adverse events are uncommon. They're well characterized, and they're adequately reflected in the current labeling.

It is important to recognize that the products we're talking about have two distinct use patterns with distinct risk-benefit profiles. Aspirin and the NSAIDs are used OTC for pain relief and fever reduction. The OTC use is short-term. We will show you data this morning that demonstrates, that demonstrate that the risk associated with these ingredients in the OTC setting is low. Furthermore, the adverse events are well characterized and the current labeling is adequate and sufficient.

Aspirin is unique in that it is also used for life-saving indications related to cardio-vascular disease prophylaxis. We will show you data this morning from a large database of randomized controlled studies that clearly demonstrate the favorable risk-benefit in these indications. Here, again, the adverse

events are well characterized and described in the detailed professional labeling for this indication.

This slide highlights our agenda for today. We will begin with Dr. Jerry Faich who will discuss how to evaluate the safety of analgesic ingredients, and Dr. Faich will address a number of the questions that were discussed by the Committee in the session just following. In the interest of meeting Bayer's 30-minute time frame, we're going to move directly from Dr. Faich to Dr. Hennekens. However, Dr. Fries is available for the question session.

DR. FAICH: Good morning, ladies and gentlemen. I'm pleased to be here and have an opportunity to discuss what is indeed a very important topic.

I'd like to start out and just go back to some fundamentals about what we're doing here for a minute and just point out, as you all well know, that drugs don't have toxicity sitting in a bottle. The toxicity is related to the inherent properties of the drug, but equally important, how it's used, by what population, what the risk factors are in that population, how long the drug is used. And those factors are critically important as you all evaluate the data that's being presented today. You've talked

about this already, the issue of extrapolating from prescription use in let's say a Medicaid population, to OTC use has to be done cautiously, shall we say, because it is an extrapolation and I think we all recognize that.

Obviously, any evaluation from epidemiologic data or, for that matter, clinical trial data, is going to be dependent upon how much we know and how carefully we've collected data about patients, outcomes and exposure. And in particular, one's got to ask what was the relationship, even in observational data, with disease severity. How severe was the arthritis or the pain being treated, because if that's related to the potential risk of GI toxicity, one has to take that into account.

That becomes particularly important because we're talking about two patterns of indications; in large part, the long-term studies of prescription OTC, prescription NSAIDS, are anti-inflammatory use as opposed, in arthritic patients, obviously, as opposed to short-term analgesia use.

What I'd like to do then is just talk about what we know in terms of naproxen and aspirin randomized trials, then go on and mention a few things about observational and come back to spontaneous reports with those thoughts in mind.

Well Nick Moore, who is here, has done, I think, one of the largest studies of OTC-type use of the analgesics we're considering here in France. This was a study published in 1999. He used eleven hundred general practitioners who used either ibuprofen, acetaminophen or aspirin for up to seven days, for the usual common painful conditions, musculoskeletal, et cetera.

This was a blinded randomization of about 9,000 patients and what the study found, and it was largely, it turned out largely to be a study of tolerance for ibuprofen, acetaminophen and aspirin to GI-adverse events. And these were all relatively minor, dyspepsia-type events where four percent, five percent, 5.3 percent and 7.1 percent, respectively.

I show you these data mostly for this last line. There were only six non-serious GI bleeds, four for acetaminophen and two for aspirin.

And the take-home message here is even when you study 3,000 patients per arm, you're not going to learn very much about relatively uncommon or rare GI bleeding events, not least because of the short duration of therapy, so the total amount of person time observed is relatively short.

On the other hand, this is probably the largest study that looks at OTC analgesia that I know

of.

If we look at the meta-analysis done for naproxen, OTC, a published meta-analysis that looked at 48 randomized controlled trials using naproxen, again, at OTC doses, usual indications for pain studies B dental pain dysmenorrhea, cough, cold, musculoskeletal, 45 percent of these studies were single-dose studies, which may not be totally inappropriate given that we're talking about OTC usage to begin with, and 55 percent were multiple dose. Four thousand naproxen patients; 2400 placebo patients; again, tolerability B dyspepsia, nausea, vomiting, one, three and one percent, no difference from placebo. And no serious SAEs, GI-wise.

So where do we go if that's what, if that's the nature of the clinical trial data we're going to look at, and I think it gives us some assurance that the rates of the events that are of great concern to the Committee today are, indeed, quite infrequent. Obviously the place to go is observational studies. And you've been hearing a good deal about that this morning. And I salute the presentations.

It has to be said, once again, that what you've been looking at in large cohort studies and even in case-controlled studies, is limited or no

ascertainment of OTC. The way you construct a large cohort is you go into a transactional claims database, like Medicaid, or you go into a medical record-link database, like General Practitioner Research Database, and, almost by definition, you do not get OTC usage.

The other thing that has to be said, going back to my first slide, is the populations indeed are different as well. And elderly Medicaid population probably will, it will tell us a good deal studying that population, about elderly patients with arthritis, but it may be of lesser value, not no value, certainly not, but lesser value in terms of extrapolating.

I would like to come back and talk about what, three specific data sources. General Practitioner Research Database was a case control study that has been mentioned this morning and I'd like to go to it in a minute.

ARAMIS is a very large, ongoing study of arthritis patients. There are 49,000 patients in that database which, I might just say, shows very little difference in the GI outcomes for aspirin, acetaminophen and low-dose NSAIDS, and, as was mentioned, Jim Fries is here to present or talk about those data if we have time.

Brian Strom and Jim Lewis at the

University of Pennsylvania are right now conducting a case control study with, paid for by Bayer, with a major focus on making sure that we have appropriate ascertainment of OTC doses. And I might just say, as mentioned, enrollment for that case control study is going slowly and the reason it's going slowly in the Delaware Valley is it does appear that GI bleeding, major hospitalized GI bleeding rates are going down as a secular trend, as was mentioned here today, partly, obviously, because of the use of proton pump inhibitors, maybe a lower threshold for doing endoscopy and a whole variety of things, not least maybe is the use of selective Cox-2 agents. So that also is the context into which we're talking about OTC usage.

Here is that Garcia Rodriguez paper, once again. I would point out that these are quite reputable investigators. The General Practitioner Research Database is a well-developed research tool. It is a medical record link system in the U.K., and what was done in this system, it covers on the order of six million person years of experience, capturing again all prescriptions and all outcomes, was that Luis Garcia Rodriguez collected 2,100 cases of upper-GI complications, very large case control study. Eleven thousand controls, and here, to correct

something that was said earlier, he did adjust in his analysis for those risk factors that are known including age, sex, calendar year and, importantly, use of aspirin, use of omeprazole, prior GI history. So what he was going after here is to say, gee, am I, have I controlled for those things that might drive selective or confounding by indication and selection?

And this is what he found. For acetaminophen, under two grams, the relative risk here is .8 B 1.9, depending on the exact dose. So there was no increase in risk against non-users of these products. For acetaminophen greater than two grams, surprisingly, relative risk of 3.6. Again, that's an adjusted relative risk. And for low- to medium-use NSAIDs, 2.4; high-dose NSAIDs, 4.9.

So again, as Marie Griffin showed this morning, there does appear to be some dose response relationship, which, if you extend down, even at the lower end of this B maybe a bit lower than this B but there is increased GI bleeding in the use of NSAIDs, even at low doses, but it gets to be a lower rate as you drop the dose. Again, thinking about OTCness here.

How do you explain, then, the surprising finding of acetaminophen here actually? I would contend that it could be some residual, uncontrolled

confounding, but it also might be, as I alluded to before, the fact that high-dose acetaminophen might be being used for patients who have a considerable amount of pain, or arthritis and that, in turn, might be linked to the GI bleeding.

That is, it may not be just a Cox-1 effect of the drug and, as was pointed out, we do have to be mindful that there's a background rate of GI bleeding in what will be the NSAID/analgesic-taking population.

The other thing that's important about the Garcia Rodriguez paper is, as far as I know it's the only one that actually has collected, in a systematic way, with internal validity, acetaminophen, not only exposure but dose data itself.

Well, let me mention a few things about spontaneous reports and then I'll wrap up. FDA, in its briefing document did point out that it's received over the last four years on the order of 541 cases of GI hemorrhage, ulceration or perforation, with 29 deaths, for aspirin.

It's important to emphasize that, when you look at those cases as FDA did, and these are largely, these are their data, risk factors were present in 90 percent, and I've listed them here: steroids, anti-coagulants, alcohol use. The age was at 69; mean exposure was beyond the usual OTC analgesic dose and

the reason for that, of course, is 70 percent of these cases were exposed to aspirin probably for cardio-vascular prophylaxis.

So, as was mentioned, one has to say in looking at these, you've got to go back to clinical trials, if you're fortunate enough to have them and ask, what's the risk-benefit equation in these patients and that's exactly what Charlie Hennekens is going to review for you in a few minutes.

For naproxen, there were 73 cases where naproxen was, to the spontaneous reporting system, again, same four-year period, where naproxen was the primary suspect drug. Risk factors, again, were present in 76, in 70 percent of these cases. They were relatively elderly. Duration of exposure was more than seven days for half of them, so this becomes an issue presumably of labeling, or these were patients who were taking OTC drug for non-OTC indications, or in a non-OTC manner. And again, half of these reports were consumer reports, so we have to ask how good is the data?

So let me summarize what I've said here very quickly. First of all, I would contend that existing clinical trial data don't provide us much information on rare, serious events for OTC analgesic use. And we're going to have to get there by

extrapolation and using observational data.

Observational data are limited in terms of their direct applicability to OTC, but on the other hand, they do suggest that there's relatively small differences between one OTC analgesic and another, acetaminophen excepted, but again, that may be a phenomenon that is not represented in the database.

The other thing I would like to say about that before I leave that point is Marie Griffin nicely pointed out that the background rate of GI bleeding is on the order of four per thousand person years, again, in the Medicaid database. And that's the background rate at low-dose NSAIDs.

If I heard the numbers and looked at the data closely, that rate goes up to six to eight. So it's on the order of double, six to eight, but it's per thousand person years. We are talking in OTC, in the OTC arena, of taking those thousand person years and breaking that down into 50,000 person weeks with the same numerator, if you will.

It's not quite the same but the point is that still we're talking about per-unit exposure, an even rarer rate. And, of course, that has to be there if we're going to talk about OTCness for these compounds.

And then lastly, I would contend that

spontaneous reports really don't allow for comparative risk assessments. I think they are, they give us some signals, some sense of who's at risk and what we find when we look at that is that the populations who get into trouble with OTC use of analgesics are the same populations who get into trouble with prescription dosing.

Thank you very much.

Charlie Hennekens is going to come up and then I guess we'll take questions at the end.

DR. HENNEKENS: Thank you Gerry.

I've been asked to speak with you about the benefits and risks of aspirin in the treatment and prevention of cardiovascular diseases. And fortunately here we have a very large and conclusive body of evidence from 199 randomized trials that have included over 267,000 subjects, over 200,000 in 194 secondary trials, and 67,000 in five primary prevention trials. These trials included average durations of treatment and follow-up of three to five years, predominately with aspirin, but some including other anti-platelet drugs.

The doses of aspirin studied ranged from a low in a Dutch trial of transient ischemic attacks of 30 milligrams a day to doses over 1,800 milligrams a day in the early trials of the treatment of stroke.

Now the benefits have been demonstrated in doses from 75 milligrams a day upwards. In fact, in meta-analyses of the dose, patients who received less than 75 milligrams a day in the few trials that were done had a non-significant benefit of 13 percent, plus or minus eight, versus a 25 percent, plus or minus two benefit B clear, significant benefit B for all the other doses and nod significant heterogeneity in benefit at the higher doses studied. And this was on the end point of important vascular events, a composite of non-fatal myocardial infarction, non-fatal stroke and cardiovascular death.

In the secondary prevention patients and acute MI patients, aspirin has been approved by the FDA to decrease the risk of MI, which it does by about 33 percent, stroke which it does by about 25 percent and cardiovascular death which it does by about 15 percent. So all secondary prevention patients, with prior MI, with unstable or stable angina, who had PCIs, bypasses, occlusive strokes, or TIAs, are recommended for aspirin treatment, although, interestingly, only 50 to 80 percent of these patients are currently being treated. And the dose recommended in these patients is 81 to 325 milligrams daily.

In acute myocardial infarction patients, aspirin is also recommended for all of those who come

in within 24 hours of onset of symptoms of the acute MI of which 40 to 70 percent are currently being treated and the dose recommended is 162 to 325 milligrams, initial loading dose. This is because of work from Garrett Fitzgerald on healthy volunteers and those with unstable angina, showing that while a dose of 75 milligrams a day would inhibit thromboxane B-2, the stable degradation product of thromboxane A-2, the time course of that degradation and inhibition is over two days. So one needs a dose of probably 325 to get the most rapid clinical anti-thrombotic effect in the acute syndromes.

With regard to the utilization pattern in these patients in an analysis led by my colleague, Nancy Cook, we found that only 40 to 50 percent of patients who were eligible for aspirin therapy were actually on it. And perhaps more strikingly, of those who thought they were taking aspirin, 80 percent were taking aspirin; another 10 percent were taking NSAIDs and a final 10 percent, acetaminophen.

In primary prevention, in this year aspirin has become recommended to decrease the risk of a first MI, which it does by about 32 percent, by the American Heart Association, for all men and women whose 10-year risk is greater than 10 percent. The Primary Prevention Task Force published these

recommendations in July, in circulation, of this year. And earlier this year, by the U.S. Preventive Services Task Force, who recommends aspirin for all men and women whose 10-year risk is great than six percent in a paper published in the Annals of Internal Medicine earlier this year. And, again, the does recommended is 81 to 325 a day.

Looking at the risks of aspirin in cardiovascular disease, both the relative and absolute risks are low. The point estimate for GI distress is about 1.2, with absolute, of the relative risk, with absolute risk ranging from about 4 to 14 percent. GI bleed is about a 1.6 relative risk, with absolute risk between one and 4 percent. And cerebral hemorrhage, a relative risk about 1.6 with absolute risk ranging between one and two per thousand.

Here I think randomized data are really necessary to provide the most reliable evidence for small to moderate benefits or risks due to inherent biases and uncontrollable confounding that's inherent in the observational epidemiologic studies. I say this, of course, with the caveat that for most hypotheses, randomized evidence is neither necessary nor desirable. But, however, for small to moderate effects we really need randomized evidence; in fact observational studies have mislead is again and again

for small to moderate effects.

There are a large number of well-designed, well-conducted observational studies, case control and cohort, showing significant clinical benefits of post-menopausal hormone use or Vitamin E and of Beta-carotene, and the randomized trials have not supported this benefit.

So looking at the individual trials that look at the cardiovascular risks of aspirin, I think the best, perhaps, is the U.K. trial of transient ischemic attacks. Two thousand, four hundred and thirty-five patients were enrolled in a randomized, double-blind, placebo-controlled trial, whose average duration of treatment and follow-up was four years. The dose was compared with 300 milligrams a day and 1,200 milligrams of aspirin daily versus placebo. And, as you can see for GI discomfort in the placebo group, 25 percent of patients reported GI upset. When people think they're taking aspirin, they will report GI discomfort and that's why one needs the randomized, placebo-controlled designs, to get the best estimates of the true rate of side effects attributable to the drugs.

In the 300 milligram dose, the rate of reporting of side effects was 29 percent and in the 1,200 milligram dose it was 39 percent. So while the

dose of 300 milligram versus placebo was statistically significant, the difference between the high dose and placebo, as well as between the high and low dose group, was also statistically significant.

For GI bleeding, the rates were 1.6 percent in the placebo group, 2.6 percent in the 300 milligram group and in the 1,200 milligram group, 4.9 percent. So while the benefits seem to be similar across a range of doses, there is a dose response relationship for GI discomfort and bleeding, although the absolute risks attributable to aspirin are reassuringly low.

So in summary, in randomized trials of secondary prevention and acute myocardial infarction, and these are patients whose ten-year risks of subsequent events are from 20 to 50 percent, the cardiovascular disease benefits of aspirin far outweigh the risks and FDA has approved aspirin for these indications.

In the randomized trials of primary prevention, in patients whose ten-year risks are greater than six percent according to the U.S. Preventive Services Task Force, or ten percent according to the AHA, here the cardiovascular benefits of aspirin also outweigh the risks. The daily doses demonstrated benefits range from 75 milligrams upwards

to 1,800 milligrams a day. Keep in mind that in assessing these, the observational studies do have these inherent biases and uncontrollable confounding in attempting to evaluate the benefits and risks of aspirin in cardiovascular disease.

In addition, we should be cognizant of the fact that there is underutilization and mismedication with aspirin in the treatment and prevention of cardiovascular disease. Others have estimated that the more widespread and appropriate use of aspirin could avoid over 10,000 premature deaths in secondary prevention and over 100,000 first MIs in primary prevention in the U.S. each year alone.

So, in conclusion, I feel that based on data from these large numbers of randomized trials of aspirin, both individually as well as in their meta-analyses, the cardiovascular benefits outweigh the risks in secondary prevention in acute MI, and remember we're talking about absolute risks of 20 to 50 percent over ten years, as well as in primary prevention in men and women whose ten-year risk is greater than 10 percent according to AHA and our anti-platelet trial as collaboration, or over six percent according to the U.S. Preventive Services Task Force.

The relative and absolute risks of aspirin are low and, indeed, much lower in the trials than

those reported from the observational studies and the randomized trials provide very reliable estimates for the benefits and risks of aspirin in cardiovascular disease.

One final comment. In the FDA adverse event reporting system, Dr. Faich has noted that 68.9 percent of the GI bleeds were for cardiovascular uses and, of these, over 90 percent had risk factors for bleeding and particular prior histories of bleeds, use of warfarin and steroids, raising the possibility of the need for much better education of health care providers and their patients.

So in conclusion, there's a large body of randomized data providing very reassuring evidence that aspirin has a very favorable benefit to risk ratio in the treatment of cardiovascular disease. Indeed, my own view is that we have a major clinical and public health challenge in the United States for the more widespread and appropriate use of aspirin in the treatment and prevention of cardiovascular disease to avoid premature death and disability.

Thank you very much for your attention.

Dr. Heller.

DR. HELLER: We have shown data that demonstrate the favorable risk-benefit for aspirin and the NSAIDs in OTC use, as well as the favorable risk-

benefit for aspirin use for cardiovascular disease prophylaxis. For both uses, the adverse events are well characterized and they are adequately reflected in labeling. Thus, we believe no further warnings are warranted.

Based on the under-utilization of aspirin for cardiovascular indications, additional warnings on aspirin, if they are not clearly justified, could have a negative effect on the physician-guided, life-saving uses of aspirin, with a detrimental effect on public health.

Thank you. This concludes Bayer's presentation and we are ready for questions.

DR. CANTILENA: Thank you, Dr. Heller. Thanks to your team for an on-time presentation. We are now able to do questions to Bayer and their team and we'll open it up.

Dr. Laine, Dr. Brass.

DR. LAINE: I have two questions, kind of one, general process, one specific.

Dr. Heller suggested that it's not appropriate or proper for us to kind of ignore the fact that patients take NSAIDs longer, low-dose aspirin, longer and at higher doses than is recommended in the label. And actually, I'd like to ask the FDA if that's true, if there is some

regulatory issue here.

My view, as a non-member of the NDA sitting as a member of the Advisory Board, I would actually pay attention to what patients do. We know a significant number of people do take them for longer and at higher doses, but is there some regulatory issue I should know about that I'm not supposed to pay attention to this fact and only look at the risk with it as labeled?

DR. GANLEY: No, you can look at that fact.

DR. LAINE: Okay, thank you. The second issue is actually for Dr. Heller.

Aspirin, as I look at the label, is recommended up to four grams a day and, we really haven't talked about it, but to my knowledge, four grams a day of aspirin is kind of the prescription dose and has similar GI outcomes to the prescription doses of traditional NSAIDs and that seems to have been kind of glossed over. And I just wanted to see if you don't, if that's an incorrect statement on my part.

DR. HELLER: I think there were two aspects in your saying that four grams a day is the maximum OTC doseC

DR. LAINE: I know, short duration, right.

DR. HELLER: That's for sure, and it's for short duration. I think the second part of your question is regarding the risk at that dose specifically?

DR. LAINE: Well, my feeling is that four grams is associated with a relatively high risk of GI events, similar to prescription doses of NSAIDs, albeit I admit, when given longer term. There are fewer data on seven days.

DR. HELLER: Let me ask Dr. Faich to comment first on that question in terms of the risk at that dose.

DR. FAICH: I think the reality is we really are very much lacking data, as you well know. And that's, that was the point I was trying to make. As I mentioned before, the fact that aspirin is OTC means it really doesn't, isn't resident in most of the linked, automated claims data bases that are going to allow us to study it.

So, the short answer it, I think you may well be right. We're just lacking data. Short-term use, however, you know, it's an issue of dose over time as well.

DR. LAINE: I would agree with the seven days we're lacking data, although certainly endoscopic studies are quite dramatic at seven days. But we

certainly have data on that dose of aspirin being, having typical rates when given for longer times anyway, I would suggest. And there are good data on the longer duration, but not on seven days.

DR. FAICH: Yes, and as you and I both well know, and I know it from the classed trial as well, that the correlation between endoscopic findings and clinical events is non-linear.

DR. CANTILENA: Okay, thank you. Dr. Bass.

DR. BASS: Yes, I'd actually like to follow up Dr. Laine's opening comment because I found the presentation actually kind of interesting but not terribly relevant. And that, if I go back to your opening remarks, you said that when used according to label, the drug is safe and that we have been confronted with evidence that it is not consistently used according to label. And so that leads me to ask you, do you disagree with the conclusion that it's not used according to label by a substantial fraction of consumers and, if you do agree with the conclusion, do you believe it is not a health problem or do you believe that there's no labeling changes that might modify those behaviors?

DR. HELLER: Yes, let me clarify. What I have intended to convey is that in considering risk,

that the risk of OTC use being intermittent and short-term should not be mixed in terms of understanding and assessing that risk with long-term prescription.

And primarily, it was my intention to make the distinction particularly with aspirin, where aspirin has, wears two hats as it were, and that the risk and events that are clearly associated with the cardiovascular indications, which are life-saving, ought not to be confused with the OTC.

The questions that you, the question that you ask, which I think is really on a different topic and it certainly was not my intention to convey a position as to what number of people may, in fact, be using these OTC drugs, or any OTC drugs, beyond the restrictions of labeling. So that was really, there was no intention of our making an assertion about to what extent the American public may, for all OTC drugs, be in fact using them not in accordance with labeling.

DR. BASS: But you did conclude that no labeling changes were required. And that conclusion is one I'm trying to understand the basis of, because it certainly wasn't addressed in the data you presented and it's superficially contradictory to other data we have heard.

DR. HELLER: The conclusion is based on

our position that the adverse events are well known and that they are adequately covered in the label.

DR. CANTILENA: Okay, thank you. Dr. Rumack, did you have a question? Dr. Cush, did you have a question? Not yet. Okay. We'll take a pass. Dr. Davidoff.

DR. DAVIDOFF: Yes, I wanted to just comment on the interpretation of RCT data versus observational data because we've heard a good deal about the various values of the different types of studies, and I will certainly not yield to anyone in my defense of the RCT as being a powerful instrument.

But I think that, I get concerned when observational data, in a sense, are put in this hierarchy of sort of further down the scale. I think that's unfair and inappropriate in the sense that, while RCTs are clearly much less susceptible to confounding, they are also biased. They are biased because they are less generalizable; they exclude the very, many of the very patients who are going to be taking these various drugs or undergoing various medical interventions in the real world.

Observational trials tend to extend to those patients and therefore, in that sense, are more real, realistic, more generalizable, but obviously more confounded. I would therefore encourage us all

to think of observational data and RCT data as being mutually complimentary. The best observational trials do generally produce the same results as the RCTs, as exemplified in a recent meta-analysis, best observational trials of hormone replacement, published in Annals recently, which came to the same conclusion as the current RCTs. So I think it's important that we think about these different types of evidence as being useful in two different and complimentary ways, rather than that one sort of trumps the other.

DR. CANTILENA: Okay, can we move to a question from Dr. Johnson?

DR. I have a question that's relative to NSAIDs, not aspirin, and I'm really sort of thinking about GI risk and the increase of risk with age. And so my question is, do you have data on the OTC use patterns by age? So, you know, of all of the tablets purchased in the U.S. for naproxen, what percent are purchased by 20- to 40-year-olds, et cetera?

DR. HELLER: Yes, we are not prepared here with data on the, to answer that question. That is, we do not have the age distribution for use.

DR. JOHNSON: Okay.

DR. CANTILENA: Dr. Cryer.

DR. CRYER: Part of, much of your discussion focused on the need to focus on prospective

data. I would agree that overall the risk-benefit assessment of aspirin is very much in favor of its use, particularly for cardiovascular disease. There are fixed toxicities, however, that I strongly believe that are inherent in the properties of aspirin that we have to accept for the time being.

Looking, one of the pieces of prospective data that was particularly concerning to me, which was not reviewed by you, but one which was recently published in the New England Journal of Medicine two months ago. "Prospective evaluation of low doses of aspirin, 100 milligrams to 150 milligrams, which revealed 15 percent incidence of recurrent upper gastrointestinal bleeding by year." If that is so, I think that that prospective information certainly merits some consideration as it might relate to labeling considerations in today's discussion.

My specific question, any maybe it should be directed to Dr. Hennekens is, again, I agree about his conclusion with, about the risk-benefit ratio with aspirin at the cardiovascular protective doses. I was wondering whether you might have an opinion about that same, about the risk-benefit ratio of aspirin at higher doses, for example, one gram or higher per day.

DR. HENNEKENS: Well, the point I was trying to make is that the benefit-to-risk ratio for

patients whose absolute risk is greater than ten percent over ten years is really favorable for aspirin, both at low and higher doses. I do think that I would rely on the randomized evidence to make that assessment, and the point, I agree with Dr. Davidoff completely, that the randomized evidence and the observational data provide complimentary pieces of evidence, but I think we should rely on the randomized evidence.

For looking for small to moderate effects, we should rely on the observational studies. For looking for exposures of longer durations, then we can reasonably study in the trials for moderately large effects.

So, here I think if one looks at the data in randomized trials, one sees a very favorable benefit-to-risk. If one looks at some of the observational studies, one may see some similar trends but larger absolute risks that I think are related to the inherent biases and uncontrollable confounding in those particular studies.

DR. CRYER: All right. And then, I just wanted, if I may, ask one additional question. To get back to Dr. Faich's comments about the general practitioner database which supports their comments about acetaminophen. I mean, my understanding of that

paper really is that medical histories were not provided and I think the consequence of not having a detailed review of medical histories is that there is this potential for confounding by indication.

I think it's very likely that higher risk patients were given acetaminophen, and in particular I think it's important to understand whether that acetaminophen was given before the, a history of an ulcer or as a consequence of having a history of an ulcer. And I just, the comment, I guess, specifically is that, do you really believe that acetaminophen is associated with the risk associated in that paper?

DR. CANTILENA: Is that a comment or a question?

DR. CRYER: The question was, was about the risk related to acetaminophen and his opinions about it.

DR. FAICH: As to the quality of the records, it is a medical record-based system. It's an automated, computer-based-- That is, the data derived from literally the doctor's record, there's an enormous amount of data there, so I don't think that this was the question of an insurance claims diagnosis by any means. And there is longitudinal data on each patient, so you can profile the patients.

You are right that Garcia Rodriguez did

not go out and individually validate all of the upper GI complications in the study, much like Marie was talking about, about going back and revalidating the exposure history. But that's been done in this database before, and so if you're diagnosed as a GI bleed, you usually have a GI bleed-- And also the quality of the records has been validated.

Now, on your point about do I believe the result? I too was surprised by this result. I do believe as well that some degree of confounding by indication, being concerned that a patient with a prior GI history should selectively get the drug that's perceived as not being gastropathic, contributed to this finding.

The question is, do I think that's enough to fully explain it, and my answer is no. So that's a, in between those two things. I think some of it's real.

DR. CRYER: Thank you.

DR. CANTILENA: Okay. Dr. Lam.

DR. LAM: This question is for Dr. Faich. Now in one of your earlier slides that present the randomized controlled trial of aspirin, ibuprofen and acetaminophen by Moore, et al., the data showed that the total GI events for those three drugs was from four to 7.1 percent. What is the age range of the

patients and are there other concurrent risk factors present in the population?

DR. FAICH: I'm going to ask Nick Moore who's sitting right here to answer the question, since it's his study. Is that all right?

DR. LAM: Yes, sure.

DR. MOORE: The age range was above 18. Concomitant risk factors were anything that was within the labeling. I mean the inclusion/exclusion criteria for that study was the labeling of the drug as it was legal at that time.

DR. LAM: So the range of ageC

DR. MOORE: Above 18. I think we set our cutoff point at 75.

DR. LAM: Okay.

DR. MOORE: Four percent had previous history of GI disorders.

DR. CANTILENA: Okay, thank you. Dr. Neill.

DR. NEILL: A couple of questions for Bayer.

Later this afternoon, I think we're going to spend some time speaking about labeling, and so both of these are about labeling.

Right now, for aspirin and the other NSAIDs, there's an alcohol warning which includes as

its last sentence, "Aspirin may cause GI bleeding." The other NSAIDs have a similar warning. Look, seeing evidence that suggests that that's independent of its use with alcohol, should that, should we consider a separate, distinct warning, separated out from the alcohol warning? Do you want to answer that and then I have one, another unrelated question.

DR. HELLER: Sure. Yes. We believe that our labeling, actually, Steve, do you want to read what, just for, we'll read what's on the label.

DR. WEISMAN: For clarification for the Committee it may be helpful me to just read out loud the labeling that is on aspirin. You referenced the fact that the alcohol warning does say that aspirin may cause stomach bleeding, but in addition it does reflect on the drug facts label, that "Ask a doctor before use if you have bleeding problems, asthma, ulcers, stomach problems such as heartburn, upset stomach or stomach pain that persist or recur." And furthermore it says, "Ask a doctor or pharmacist before use if you are taking a prescription drug for anticoagulation, thinning of the blood, diabetes, gout or arthritis."

DR. NEILL: So, I don't know if you would favor a separate warning or not.

DR. HELLER: Our view is that the current

label is appropriate, but of course, we view these proceedings as a partnership with the Committee and with FDA, and we would certainly consider carefully any recommendations from this committee.

DR. NEILL: The second question has to do with the guidance that we have been given by FDA staff about aspirin. Because aspirin is used chronically, and I as a doctor am going to instruct my patients to take this, take it every day, buy it over the counter, one of the things that I need guidance about is why aspirin, when prescribed in that way, should be exempt from the same sorts of risk information that is provided to patients when they go to a pharmacy, for example, from getting other prescription medications.

Should it be distinct? Should there be additional information that is required to be provided when they pick up aspirin for chronic use at the prescription of a physician? If not, why not?

Please understand, I did hear the information about benefit-risk, but that is something that each individual consumer is going to need to make an informed decision about, which is something that we inform them about by the prescription process. If aspirin is not subject to that same kind of information process, should it be and, if not, why not?

DR. NEILL: Again, we believe that the current labeling is appropriate. I appreciate that you raise, to my mind, a pretty complicated public health issue. We are completely in agreement with you that we want labeling that optimally protects the consumer across all uses, and I think the question that you raise -- I don't think that my personal opinion on that is really of value. I think this the kind of question that the committee needs to deal with.

It is our belief that the current labeling is optimally in the interest of the consumer.

CHAIRMAN CANTILENA: Okay, thank you. For the individuals who haven't had a chance to ask their questions, we will have that opportunity right after lunch to talk again to all the sponsors who are here.

So we will now thank you for your time and staying on time, and as we try to do the same thing, we will now move to the presentation from Wyeth, which will be led -- It will be a 20 minute presentation, and it will be led by Dr. Berlin. Dr. Berlin.

DR. BERLIN: Good morning. I am Roger Berlin, President of Global Scientific Affairs at Wyeth Consumer Health Care, developer and NDA sponsor for the Advil brand of OTC ibuprofen.

I would like to thank the committee for

the opportunity to address them this morning.

Wyeth Consumer Health Care recognizes its responsibility to the consumer to provide OTC products that are effective, have a favorable benefit-to-risk ratio, are manufactured to high quality standards, are promoted responsibly, and that are labeled in a manner to maximize appropriate use.

We believe that Advil products meet these high standards, but we recognize that evolving knowledge may permit further improvement to the label. We are committed to a positive collaboration during this hearing and in subsequent interactions with the FDA in addressing recommendations you may offer.

Following OTC approval under an NDA in 1984, we have sponsored and conducted an extensive program of clinical and epidemiologic research to expand our knowledge of the tolerability and efficacy of Advil, and have fulfilled NDA requirements to report all serious adverse events. Based on the totality of this data that we accumulated, we filed in November of 1997 a citizen's petition to include ibuprofen in the analgesic monograph.

In its recent response, FDA states, and I quote, "It believes ibuprofen 200 milligrams has been marketed safely for a sufficient time and extent that it can be generally recognized as safe and effective

for OTC use."

A favorable benefit to risk ratio is critical for an OTC ingredient. However, no drug is without the potential for adverse outcomes, especially if misused or abused. Every drug has the potential to cause unintended effects in certain target organ systems. Potential effects of ibuprofen use on GI and renal systems were critically considered at the time of the initial ibuprofen OTC approval and label development.

The maximum daily dose of 1200 milligrams a day is only 37.5 percent of the maximum daily prescription dose of 3200 milligram, and the maximum duration of use is ten days for pain and three days for fever. This is in stark contrast to high daily dose extended duration prescription use.

GI and renal safety are improved dramatically when one compares OTC doses and duration with those of prescription use. Data from prospective, well controlled clinical trials, large scale epidemiology studies and adverse event reports indicate the following conclusions.

Ibuprofen is the safest NSAID. Serious GI adverse events occur at or very close to the background rate in OTC use, and that serious renal adverse events are uncommon. Supporting data are

provided in the background package.

It is critical not to blur the clear distinction between OTC and prescription use safety profiles. Ibuprofen has a large therapeutic index, and AAPCC data demonstrate the safety advantage of ibuprofen in overdose.

Consumer research and actual use clinical study data indicate that the vast majority of OTC consumers use the product in conformance with the label instructions, and I can go into that data later. The label repeatedly instructs consumers to use the minimum effective dose. Specifically, the directions recommend initiating treatment with one tablet, increasing to two if needed, and it goes on to say do not take more than directed, use the smallest effective dose.

Called out under the alcohol warning is the risk of stomach bleeding. There is a statement to ask a doctor before use if you have stomach pain, and to stop use if stomach pain occurs with use of the product or any new or unexpected symptom occurs. Consumers are directed to ask a doctor or pharmacist before use if taking another product containing ibuprofen or other pain reliever or fever reducer or if they take drugs on a regular basis or are under the doctor's care for any continuing medical condition.

The current label for Advil has been very effective in ensuring the safe and appropriate use of the product in over 18 years of use with over 100 billion tablets. A recent label comprehension study of the current drugs facts, format Advil label, which included those of low literacy and the elderly, confirms that the communication goals are very successfully met.

Interestingly, about two-thirds of the current users have consulted with a physician about their use of Advil.

Based on the use experience with this current label, the FDA has determined that ibuprofen should be recognized as generally safe and effective. However, the FDA proposed modified GI and renal warnings in the monograph notice, and we have displayed these in your background package, versus the current label.

We are supportive of changes that would further enhance safe use of the product by the consumer. However, any alterations to the label should be tested with the consumer to ensure they achieve the intended communication goal. We are committed to continue to work with the FDA to develop the best possible label.

I will now turn the podium over

sequentially to Doctors Sica, Walson and Weisman. Thank you very much for your attention.

DR. SICA: Thank you. I appreciate the opportunity to address the Nonprescription Drug Advisory Committee. My name is Domenic Sica. I am a full-time professor of medicine and pharmacology in the Department of Medicine and Nephrology ad the Medical College of Virginia campus of Virginia Commonwealth University in Richmond, Virginia.

Based on my training and extensive experience, some 25-odd years of clinical practice and nephrologic research, I am here to discuss the likelihood of renal toxicity associated with the use of OTC ibuprofen and whether changes to the current labeling for OTC ibuprofen would relevantly address these risks to the consumer.

In the past I have provided consultation to a number of pharmaceutical companies, fewer these days, on the safety and efficacy of various drugs. Some of these companies have included Merck, Bristol-Myers Squibb, Pharmacia and Wyeth Consumer Health Care, and I am here to present my own opinions and will be reimbursed for both my travel and time away from the University.

Ibuprofen was first approved for prescription use in the United States in 1979. So we

are some two and a half decades out from its original approval, and it was approved at daily doses of up to 3200 milligrams per day for the chronic treatment of arthritic conditions.

It was subsequently approved for OTC use in 1984, some five years hence, and the approved OTC use was 1200 milligrams per day for a ten-day time interval. With its extensive use as both a prescription and OTC product, several comments can actually be made. For the sake of brevity, I will keep it short.

The incidence of renal failure and other serious renal events are rare with use of both prescription and OTC ibuprofen. In fact, according to the agency's review of safety surveillance data over a 15 year period of time, there were an average of approximately five reports of renal failure per annum associated with ibuprofen. In over half of these cases, the duration of use was unknown or was beyond 30 days, and I think comments about duration of use have been raised by prior speakers as well.

Serious events are not usually seen with acute dosing, and I cannot overemphasize that. Rather, they are usually dose and duration of time dependent, and we are not even exactly sure if there is a linear dose relationship on this as one goes down

the dose response curve for these compounds.

Serious renal events are almost always reversible, even in the elderly or chronically ill, and I think we need not confuse the fact that acute dosing in a compromised individual may lead to a deterioration in renal function, but again reversible, versus some comments raised earlier about chronic dosing and what occurs with chronic dosing.

The reversibility events is in part due to the unique kinetic characteristics of ibuprofen, which include both a short half-life and a reversible inhibition of the psychologenase enzyme.

Serious renal events following NSAID therapy almost always occur in patients with preexisting renal dysfunction, particularly in those who are volume contracted or dehydrated or those with critical organ system disease, including, as we heard earlier, congestive heart failure, compromised hepatic function, particularly with the hemodynamic deterioration that is seen with advanced stages of cirrhosis and in those with renal insufficiency.

Although ibuprofen interacts with diuretics, current labeling already advises consumers to ask a physician or pharmacist before use if they are to consider use. I think this is the issue of continuing chronic therapy for a medical condition as

it coincides with the chronic use of a nonsteroidal.

Intentional or unintentional overdoses with ibuprofen are not routinely associated with adverse renal consequences. Although there is always room for improvement, given the extremely low incidence of reported serious renal events over the past two decades of OTC use with ibuprofen, it is my opinion that the current label continues to adequately convey the risks associated with the use of OTC ibuprofen.

I applaud the FDA's efforts to evaluate the labeling of all OTC nonsteroidals, including ibuprofen, to be sure that these drug products are used in the safest, most effective way possible. As always, any changes should be data driven and thoroughly tested in consumer studies to determine if and how any proposed label revisions would impact consumer and physician behavior patterns.

Again, thank you for allowing me the time to present my views to the committee.

DR. WALSON: Hello. I am Dr. Philip Walson. For the last 30 years I have been a board certified practicing pediatrician, and I am currently at the University of Cincinnati and Cincinnati Children's Hospital Medical Center where I am the Director of the Clinical Pharmacology Division and the

Clinical Trials Office.

I am also a board certified practicing medical toxicologist in Cincinnati. I was in previous positions Medical Director of the Arizona Poison Control Center and the Central Ohio Poison Center at the Ohio State University.

I have personally cared for and consulted on literally hundreds of children who have taken or been given an excessive dose of an OTC analgesic or antipyretic alone or in combination. Finally, I am a board certified clinical pharmacologist, based on my prior training in internal medicine which I rapidly left, preferring to take care of better patients -- that is, kids.

I do want to give a conflict of interest statement. Clearly, I am here to express my own personal opinions on the labeling of OTC relevance. I think the important thing here is the relevance. We are here to talk about labeling, and I think it is important to keep your eye on the ball.

Because of the nature of my training and experience, I have, in fact, conducted a lot of trials, ten randomized controlled trials, for example, of various antipyretics sponsored by industry, including Wyeth, McNeil, and others, and published those trials. I have also published conglomerate

studies of their safety.

I have received consulting fees from a number of pharmaceutical companies. It would probably be easier for me to make a slide of who I didn't. But today I am -- My institution is being paid for my time, and I am having my expenses paid for by Wyeth. I hope that is -- I don't own any stock in any of those companies. That has nothing to do with actually having worked for them, I might say. I just don't believe you should own stock. I don't want to do anything to change their stuff.

I do want to -- Before I go into my statement, which I think was provided, there are four points that I do want to make, and I don't have any slides, which is unusual for me, but I do want to say it. The first one is so obvious, some of the committee will clearly have already tried to say this to the rest of the committee.

Number one, children are not adults, not little adults. I must tell you that, when I hear a lot of the discussion, I keep wanting to put that slide up to some people.

Two, in the same way, not all NSAIDs are equal. There are many examples in pediatrics. The clearest one may be look at the safety of aspirin versus ibuprofen, but there are many other examples

where, clearly, NSAIDs have very different efficacy and toxicity as well as behavior of parents and children and indications. Everything about them is different.

It is amazing to me that the FDA, for example, still collects data on pediatric events without a wait, which brings me to my third point, which always bothered me, even when I was in the Department of Internal Medicine at UCSF, is that adult doctors consistently want to call amounts doses, and they are clearly not, not for children -- that's a little obvious -- not for little old ladies, which should be obvious but apparently isn't, but even -- I mean take a look at me -- for middle-aged men versus some of the other guys who you could actually see behind this counter. Amounts are not doses, and that has to be taken into account in any risk-benefit analysis.

The fourth point -- I'm going back again to relevance -- is that this idea of a risk-benefit analysis extends to everything, including a label change, and that any change in the labeling has to be done in a way that improves the public health and doesn't deprive children of effective, safe therapies or result in the use of more dangerous therapies to treat the same conditions.

With that, I clearly support the FDA that it look for labeling of these products that maximizes benefits and minimizes any risks. I must say that, when I looked at their specific suggestions, I had trouble figuring out how many of them are going to help kids, and thought some of them will hurt kids. But again, until the studies are done, I don't know that.

Labeling should not be arbitrary or extreme. It's got to be based on evidence. Equally as important, all consumers should be able to easily read and comprehend the label. For example, studies have shown that a tremendous number of children self-medicate. No one has talked about whether these labels speak to kids, and what is a child?

It is also important that labeling not appropriately deprive children of safe, effective drugs, as I have said. I don't want to go through it, because my beeper is going on. The summary of the data is very clear, that toxicity is rare in anyone, but it is exceedingly rare in children.

In fact, for ibuprofen we even say it may be possible to kill a child with an overdose, but it is very difficult. I don't want to go through the other things that are in my comment.

In summary, I think ibuprofen has been

shown to be clearly effective, especially for pain and fever in children, and it has a very large therapeutic margin, and with few exceptions ibuprofen at OTC doses is remarkably safe, and there probably aren't even exceptions in most children. Thanks.

DR. WEISMAN: Good morning. I am Richard Weisman. I am the Director of the Florida Poison Information Center and a research associate professor of pediatrics at the University of Miami School of Medicine.

I have had 20 years of experience as a poison center director, 15 years in New York City and the last five years in Florida. I have devoted much of my life to efforts designated to reduce the mortality and morbidity from unintentional pediatric poisonings.

To understand my motivation for testifying today, one has to only look at data that is collected each year by the American Association of Poison Control Centers. Although I am presenting my own opinions to the committee, I am being reimbursed for my time and travel by Wyeth Consumer Health Care.

In the past I have also consulted for DuPont, Eli Lilly and Wyeth on several occasions.

I appreciate the opportunity to address this distinguished panel on the topic of NSAID

toxicity, and in particular, on overdose data for ibuprofen. My objective today is to discuss the clinical relevance of overdose toxicity for OTC drugs and the importance of complying with labeling directions.

In the OTC marketplace, consumers take medications for a variety of conditions and symptoms. The consumer is entrusted to read, comprehend the label directions, and then to appropriately self-select and comply with the directions for use. In spite of government, pharmaceutical company, and private sector efforts, it is the unfortunate thing that there always will be some consumers who, either intentionally or unintentionally, do not follow label directions.

For most drugs, the consequences of taking too much drug are not serious, because OTC medications, by definition, are safe drugs with wide therapeutic windows or margins of safety. However, as we heard yesterday, in rare instances, even unintentional overdoses of drugs can lead to catastrophic events such as liver failure.

The overdose data for OTC NSAIDs, in particular ibuprofen, demonstrate that there is a wide margin of safety. Ibuprofen was approved for OTC use in 1984 at the 200 to 400 milligram per dose, 1200

milligrams per day for up to ten days of use.

Since 1984, over 100 billion doses of OTC ibuprofen have been consumed. So there was extensive material time and extend to critically analyze data from overdose situations. There is no exact dosage that defines a single administration overdose for ibuprofen. However, even ingesting 18 200 milligram tablets or three times the daily dosage generally only would require supportive care.

Even at single administration overdoses in excess of five grams, the literature suggests that acute renal failure is very fare and reversible. In overdose, the most serious side effects related to gastrointestinal tract and renal systems.

In contrast to acetaminophen, the signs and symptoms of ibuprofen overdose occur shortly after the incident and most commonly include one or more of the following: nausea, vomiting,abdominal pain, drowsiness, dizziness, and tinnitus.

In a vast majority of cases, within four to eight hours after the overdose symptoms subside, and full recovery is the usual course. Patients are usually sent home after a few hours of observation.

In aggregate, poison control centers see thousands of cases of drug overdoses each year. Ibuprofen cases are generally not complicated, because

of the relatively short plasma half-life and, most commonly, the only single entity ingredient of the product. Unlike some of the other OTC analgesics, ibuprofen is only available in one OTC combination, compared to 23 different combination products containing acetaminophen.

Obviously, when poison control centers are contacted about overdoses involving multiple ingredients, the overdose management becomes more complicated.

While advances in packaging and labeling have prevented some poisonings, our ability to prevent most poisonings is still elusive. Each year poison centers are still managing more than 115,000 poisonings from over-the-counter analgesics. Poison center data show that ibuprofen is the safest of the OTC analgesics for the consumer, with the lowest rates of both mortality and morbidity.

The AAPPC test summary data clearly demonstrates the wide safety window for ibuprofen. For one of the most commonly used OTC drugs, there are relatively few outcomes classified as major life threatening events, and very few deaths.

Of course, even one death is one too many, and we need to find better ways to prevent accidental overdose with all drugs. I believe that OTC dosages

of ibuprofen are safe when used as directed, and that even in massive overdose the toxicity is rarely life threatening.

Thus, my objective was to present data showing the primary issue is not the molecule itself but finding better ways to get the consumer's attention to closely follow the label directions. I understand the purpose of this meeting is to explore ways to better communicate with consumers and to encourage consumers to follow label directions.

I applaud and fully support the efforts by the FDA and NDAC. Thank you again for allowing me the time to express my views.

CHAIRMAN CANTILENA: Okay. Thank you, Dr. Weisman. We have used up our time. So we will go -- We can actually come -- if she wants the answer now or in the question period, we are happy to do that, but we will actually open the question and answer period. The panel has ten minutes, and those of you who are not able to get in, we can certainly start the afternoon off, and you will have another opportunity to ask questions. So, Dr. Johnson, would you like an answer to your question?

DR. JOHNSON: Yes, I would be interested in the answer.

DR. BERLIN: I believe your question was

what the percentage of use was of some of these products in those over 65.

DR. JOHNSON: Well, no. I mean, that's sort of part of the issue, but the use by age group. So it is predominantly use in the elderly versus younger patients.

DR. BERLIN: Well, for ibuprofen 24 percent are between age 18 and 34. Forty-five percent are between age 35 and 49. Twenty-two percent between 50 and 64, and only 8 percent are 65 or older.

Now this varies, obviously, because of the use of aspirin for cardiovascular prophylaxis. A larger percentage, about 30 percent, of aspirin use is in those over 65.

DR. JOHNSON" Right. I would presume aspirin would be most high. I was mostly interested in the NSAIDs. Thank you.

CHAIRMAN CANTILENA: Okay, Dr. Day.

DR. DAY: I have a question for Dr. Berlin. First of all, I would like to commend you for conducting label comprehension studies with consumers. That's terrific, and I would like to know a little bit more about them. You referred to them.

I would like to know how many respondents there were, and specifically, how you tested for comprehension of dosing, and were the questions

factual or inferential. So factual would be asking something that was specifically there on the label, and inferential would involve asking something where they needed to use that information to go beyond, say in a problem solving scenario.

So a sample one would be, you know, if you have already taken three tables today and it is 10:30 at night and you have a headache, is it all right to take another?

DR. BERLIN: I think we asked those questions. I'm just a poor country gastroenterologist. So I am going to ask our market research expert to address your questions.

MS. SAULT: I am Stephanie Sault with Wyeth market research.

Our label comprehension study consisted of a test among 300 respondents. We went to 20 different geographically dispersed areas to get a good mix of geographic and socio-demographic groups.

The test was done through -- primarily through scenario questioning. Consumers were read a series of scenarios pertaining to usage, and as Dr. Berlin indicates, we got very high levels of correct responses to all of them.

DR. DAY: What was that approximate comprehension rate?

MS. SAULT: Over 90 percent for most of them, and in the high nineties for quite a few.

DR. DAY: You mean for individual scenarios, but not averaged over all of them?

MS. SAULT: For individual scenarios.

DR. DAY: And how many scenarios were there, approximately?

MS. SAULT: All told, there were 25 or 30.

DR. BERLIN: But if I might, for example, you know, one of the things is what is the adequacy of the labeling, and whether it should be changed. One of the scenarios was the last time a person took a pain reliever, they developed stomach pain; and the question was would they have to see a doctor first. The answer, percentage correct was 95 percent.

So I think that some of the scenarios actually bear on the adequacy of the current label in terms of informing patients that they should, in fact, see the doctor.

CHAIRMAN CANTILENA: Dr. Rumack, Katz, and D'Agostino.

DR. RUMACK: I have a question for Dr. Weisman. We have heard that patients take ibuprofen and others longer and in greater amounts than labeled, and from your comments I would like to know how you would like to address those unintentional overdoses on

the label.

DR. WEISMAN: With respect to what?

DR. RUMACK: Taking the OTC drug for longer than the label suggests and at a greater dose.

DR. WEISMAN: One of the ways that data is reported to poison control centers is if there is an adverse event. Now poison control centers are generally contacted when there is perceived to be an overdose. So that it probably is not the most appropriate dataset to use when looking for adverse events.

While it does contain a small subset of that data, it is predominantly acute overdose information that is within that subset. Now what we have is the ability to identify and subspeciate that there are chronic overdoses listed. There are acute overdoses listed, and there are acute and chronic. In the annual reports of the American Association of Poison Control Centers, one can separate out that component for each of the available analgesics.

DR. RUMACK: Okay. You had addressed something about the label, and that's what I was trying to understand, if you thought there should be a change or shouldn't be a change.

DR. WEISMAN: It's my opinion that the current label provides information about the dose and

the duration of therapy, and what that does is, by limiting the duration that the drug is in use, reduces the probability of getting into a situation where you've got patients that are exceeding the dose or exceeding the duration.

When you are dealing with situations where people are exceeding it or attempting to utilize the drug to mimic what would have been their prescription dose, then you are going to get the possibility of seeing the adverse events that would be most characteristic at the higher dose or higher duration. But again, I think the test database is not going to be the best source for that type of information.

CHAIRMAN CANTILENA: Okay, thank you.

DR. BERLIN: If I might just add that the label instructions were actually very well understood in terms of the dosing in the label comprehension study we were just discussing.

CHAIRMAN CANTILENA: Yes, I just have a follow-up. Have you submitted that study?

DR. BERLIN: That study was just recently completed. We haven't. We would be very happy to submit that study.

CHAIRMAN CANTILENA: Okay, thank you. Dr. Katz.

DR. KATZ: Yes. From my perspective,

knowing that consumers understand the label is obviously very important, but knowing what they actually do at the medication, to me, is even more important. I wonder if you have any data as to what proportion of people buying Advil use it chronically, longer than what the label says, and also at doses exceeding the recommended label, since we heard from the submission from NCPIE that that might actually be as much as 30 or 40 -- as many as 30 or 40 percent of consumers.

DR. BERLIN: I have to say that the research that we have available is discrepant with the NCPIE results. I can't explain exactly why that is. I'll read just some typical information to help inform the committee, I hope.

If you look at various sources of data, consumers -- the average number of tablets taken per day was 3.6 tablets when they took the medication, so about 720 milligrams a day, so less than the 1200 milligrams.

If you look at the number of people who take 50 tablets, more than 50 -- I'm sorry, who take less than 50 tablets a month, 95 percent of the patients take less than 50 tablets a month. So I think from a variety of points of view, you have only a very small percentage of people who do exceed the

dosage, either in terms of the amount, the number of tablets per dose, or the amount per day or the amount of the duration.

I think one of the other things that happens, particularly with ibuprofen because of its previous prescription history, some of that is driven actually by physician recommendation that people use the medication at a higher dose for a longer duration. Obviously, some of it is people misuse the product, but it doesn't appear to be misunderstanding the label.

CHAIRMAN CANTILENA: Dr. D'Agostino?

DR. D'AGOSTINO: I'm trying to understand the logic of the label, and I'm sitting here thinking that, in fact, I may have participated in the discussions with the present label.

The one I want to go back to is that ibuprofen may cause stomach bleeding under the alcohol warning. When both ibuprofen and aspirin manufacturers were asked about the logic of that, they said they thought the label was good, and then the response seemed to be, because there was another question or there was another spot that said asked your doctor before you have stomach pain, and with the aspirin it's either problems or stomach pain.

Is there data that says that people who

develop the bleeding all came from individuals who already had known stomach pain? I don't understand the logic of where it's placed here. If bleeding can happen with individuals who don't necessarily have stomach pain, they aren't necessarily going to call the doctor and so forth, maybe it should be separated.

Could you just go back a bit in how it gets placed where it is right now?

DR. BERLIN: Actually, the development of the label is very important. There was a label comprehension study that was done under the auspices of the FDA in 1983 prior to the approval, and there were two labels, one which had very detailed organ specific warnings and one which was more general.

When they were tested, what happened is that the one that was more general directed people to see a physician more frequently, and again I just reference the about two-thirds of the current Advil users who do consult with a physician about the use.

So I think that all of these issues are not new issues. They were considered at the time of the initial approval. There were some label testing done to try to figure out what would drive a large percentage of patients to the physician for an appropriate consultation, and it is counterintuitive, but the answer seemed to be that being more general

and less specific was more successful in driving the patients to the physician.

DR. D'AGOSTINO: We'll come back to it. Thank you.

CHAIRMAN CANTILENA: Dr. Clapp.

DR. CLAPP: I am interested in Dr. Walson and Dr. Weisman's response to information about pediatric cases of ibuprofen toxicity, particularly addressing not mortality but morbidity due to renal failure, and at what doses do you find that, and what are the kilograms of the child? And as an addendum, the gentleman from the FDA did say that the data that he can recall was based on children taking the suspension, which leads us to know that it is 200 milligrams per -- or 100 per five.

DR. WALSON: Yes, a couple of things. One is I had mentioned selection bias. There was an article by Kelly Walson, et al. in *Drug Investigation* from 1993 where he said he didn't find any studies where they looked prospectively for adverse. I would direct you to that article.

We took all of the kids in the first eight studies we did with acetaminophen, ibuprofen, and looked what happened to renal function. In fact, there was a significant decrease in BUN and creatinine in kids who were dehydrated and treated for fever.

Now, to me, that's intuitive. Some people have said that is counterintuitive, but the fact is a kid who has got a fever and can't drink is dehydrated. A kid who is dehydrated and gets his fever and discomfort taken care of is more likely to take liquids. But whatever the reason, there are data there, and I don't know why that was missed.

Clearly, there are kids who have renal failure. My personal opinion is that ibuprofen in a child who has decreased renal function or renal profusion that is being supported by prostaglandin secretion is someone who is going to have a renal adverse event. So while I think it's possible, but without the data being looked at -- For example, I would ask the FDA how many of those kids were septic and febrile and, therefore, got ibuprofen but would have had renal dysfunction with any drug, including acetaminophen in severe liver disease patients. Ten percent of them have renal dysfunction from acetaminophen in overdose, not in therapeutic use.

So while I think it's possible, one, it's exceedingly rare. The histories are not adequate. They didn't -- and we got no doses. Even if they got histories, I would want levels, because both in our studies and clearly in others, a lot of them that have been published, the history a parent gives just is

often discrepant with the various powerful objective measures of drug levels at presentation.

So I think it's possible. Certainly, mechanistically it's possible. But when I look at the numbers compared to the numbers of kids, it's possible, but, boy, it's exceedingly rare. I don't know if you want to say that, too. And it's usually reversible.

DR. WEISMAN: The experience that we have seen with children that overdose on ibuprofen relates directly to its pharmacologic effect on its ability to inhibit psycho-oxygenase. If you look back at the pharmacokinetics and pharmacodynamics, that inhibition is a very transient phenomenon where you don't have a permanent inhibition of the enzyme as you would with acetylation, which you would see with salicylates.

So that what we see is that you will often see the creatinine or the creatinine clearance bump for a very transient period of time, usually returning to its baseline within 12 to 24 hours. This has become enough of a repeated phenomenon that we basically would not keep a child hospitalized if, on that initial analysis, we found that the serum creatinine had gone up, because it's been well described that this will reverse generally within a short period and come back toward normal.

DR. WALSON: One other I wanted to stress. I don't know how many of the gastroenterologists on the panel again are pediatric gastroenterologists, but while it's a general belief, and it's hard to confound general belief with data, among gastroenterologists it is very hard to find significant bleeding in a child, GI bleeding. It occurs, but again we are not talking about does something happen. We are saying, again it's a risk-benefit. How likely is it, and what are the alternatives? I think that's really what's --

CHAIRMAN CANTILENA: Okay, thank you. There's three people who have requested questions, and I will ask them how -- are these issues that can hold until after lunch or are they -- Dr. Cryer, Cush and Wood.

DR. CRYER: Mine can hold until after lunch.

CHAIRMAN CANTILENA: Dr. Cush, Dr. Wood, would you hold? Okay, thank you very much. I owe you, Dr. Wood. This is the second time that we have held you.

Okay, thank you, Wyeth. Our next presenters are from Doctors Topol and Rothman, I believe sponsored by McNeil, and they have each been allocated for five minutes, and then as a program note we will then go into the next set of individuals, also

five minutes each, and then we'll hold our questions for those four individuals from the International Ibuprofen Association and McNeil.

DR. TOPOL: Let me first start off by Dr. Rothman is not going to be presenting. I'll just the time allotted. Dr. Rothman is -- data that he was going to review has already been reviewed earlier, and he will be available for questions later.

I am Eric Topol. I am Chairman of the Department of Cardiovascular Medicine at Cleveland Clinic and also the Provost and Chief Academic Officer of that institution as well as The Cleveland Clinic or College of Medicine.

I am here out of my interest on safety in the use of aspirin in patients with cardiovascular disease, and I would also acknowledge a potential conflict of interest with respect to that my time and travel are being reimbursed by McNeil for my presentation here today.

What I want to get into is, of course, the focus on enhancing the safety. As you know, over 20 million Americans are taking aspirin as a cardio-protective agent. So the question is how can we maximize the benefit and risk. Of course, already alluded to is the fact that many more patients should be taking aspirin than are taking it today, by the

indications that have been ratified by all the major societies, including the American Heart Association, American College of Cardiology.

Well, there's a recent trial that was just published last year, the acronym CURE for Clopidogrel in Unstable Angina for Reduction of Ischemic Events. This is a very large trial, over 12,000 patients, and it was done internationally in 20 countries throughout the world.

The data are interesting, because it compared all patients taking aspirin at the doses of 75, 200, 325 milligrams, and half of those patients were randomly assigned to either placebo or clopidogrel in addition.

There was a 25 percent reduction in the year after entry into this trial with the entry criteria of acute coronary syndrome, acute ischemic heart disease for the addition of aspirin plus clopidogrel, building on the anti-platelet theme in terms of protection from ischemic events.

Now this trial, as it turns out, provides a unique look at aspirin safety and efficacy at varying doses. Now this was not a dose on a randomized basis. However, these patients were given the dose of aspirin at the discretion of the treating physicians.

So it appears to be random in that there are no demographic differences in the different dose categories, and this is an analysis of life threatening or major bleeding -- that is, transfusion requirement, hypotension, significant bleeding -- in this trial.

These data have been presented at our national meetings of the American Heart Association, and just recently, two weeks ago, in Berlin at the European Society of Cardiology. The data for aspirin -- In the aspirin-only arm, over 6,000 patients, as you can see here, the low dose of aspirin for life threatening bleeding, 1.9 percent. For the dose between 100 and 150, 2.2 percent. This in a dose response fashion increased to 3.3 percent, and increased to 3.8 percent. So a doubling of the rate of major bleeding in the patients who were getting -- as it turned out, all these patients were 325 milligrams.

This held up, this difference, which is significant, to controlling for all of the relevant demographics, age, gender, body weight, hemodynamic status at baseline, and also to multivariate modeling.

Now what is also interesting in light of the discussion earlier today regarding the use of combined aspirin and other agents such as nonsteroidal

anti-inflammatory drugs, here we saw the same trend in this CURE trial with respect to this dose response as far as efficacy and safety.

I have already mentioned about the bleeding, life threatening bleeding, but here you see both with aspirin alone, shown in red, or aspirin plus clopidogrel, shown in orange. You can see the efficacy. This is the reduction of death, cardiovascular death, myocardial infarction or stroke, and you can see that the lowest dose was associated with at least as good an efficacy as the mid or higher dose range.

Again, this combination of aspirin with another antiplatelet agent in looking at life threatening bleeding at less than 100 milligram dose, the intermediate dose or greater than 200 milligram, you can see the doubling of life threatening bleeding, whether one looks at the monotherapy with aspirin or with the combined dual antiplatelet regimen.

Any bleeding was the same type of relationship. So you can see again the rate of any bleeding in this trial was increased 100 percent, as you can see, from 1.9 to 3.9 percent in the aspirin monotherapy patients, and from 3 percent to 5 percent in those patients receiving a dual antiplatelet therapy.

Now this is important new data. It's the best data we have regarding zooming in on the low dose end of aspirin -- that is, between 75 and 325 milligrams. We have not had a trial of over 12,000 patients in which this has been assessed until this CURE dataset.

It's important also to anchor this in with the recent landmark paper in the British Medical Journal already referred to in the earlier presentation. That is, this British medical journal meta-analysis reviewed all the cardiovascular trials with aspirin and antiplatelets. It's a mammoth meta-analysis of over 212,000 patients, most of them on aspirin studies in over 287 trials.

That meta-analysis is quite relevant. As was pointed out earlier, the patients who were taking less than 75 milligrams had an insignificant, only 13 percent, reduction in cardiovascular death, MI or stroke. However, the patients who had this low dose, 75 to 150, actually had the maximal reduction, 32 percent, as compared to those patients who were between 160 and 325 milligrams, where it was 26 percent.

Note the overlapping 95 percent confidence intervals, the point being here is that not to state that the low dose, 75 to 150, is superior. The point

is that with this very large dataset, we can at least assert, and now also with the clopidogrel data, that it is not inferior.

So the efficacy is not at all compromised with the lower dose, and I believe we have very strong data now to support that, as one goes up from 160 milligrams of aspirin to 325 milligrams of aspirin, this is associated with an untoward risk of bleeding. This is obviously very important in the public health interest.

So, obviously, we have come a long ways with aspirin, and we have much more work that needs to be done regarding aspirin dosing. We are zooming in on what appears to be the appropriate range. We know that the doses of 80 to 325 milligrams are the optimal doses in patients with ischemic cardiovascular, cerebral vascular and peripheral arterial disease, but in this over 100 years of studies of aspirin and, of course, in recent decades in trying to refine the application to vascular disease -- and perhaps thematic throughout all of the discussions you have had over the last two days is understanding this appropriate balance between the effects on prostacyclin and thromboxane $A_2$.

I would submit to you, based on what we know today -- and of course, always it would be nice

to define through dedicated prospective large scale trials -- is that the doses of aspirin between 80 to 160 milligrams appear to be superior to 325 milligrams insofar as reduction of bleeding, with at least as good an efficacy profile.

So I think that is all I really wanted to contribute here to the session, and we are certainly pleased to respond, Dr. Rothman and I, to any questions that you have.

CHAIRMAN CANTILENA: Okay, thank you very much, Dr. Topol. We will hold the questions and move right to the two five-minute presentations from the International Ibuprofen Association, Doctors Langman and Moore.

DR. LANGMAN: Whatever you will be confident in, it's not of my grasp of technology.

I'm Michael Langman. I am Professor of Medicine at the University of Birmingham in England. I have taken no personal fees or compensation from industry for the past four to five years. My prior and current indirect interests through my university are recorded in the annual reports of the Committee on Safety of Medicines of the UK since 1987. My travel costs were paid by the International Ibuprofen Foundation.

Risks of acute gastric and duodena loss of

bleeding vary according to the nature of any nonsteroidal anti-inflammatory drug in use and taken overall with dose. I now present results appearing this month in the British Journal of Clinical Pharmacology which examined risks according to the dose of individual NSAIDs.

Meta-analysis of individual patient data, not summated results, was employed to combine three case controlled datasets, one from the UK published in *The Lancet* and funded by the Medical Research Council of Great Britain, one from Catalania, Spain, also published in *The Lancet*, and one from Sweden, part of a larger U.S. and Swedish study.

The overall analysis was funded by a European Economic Community bio-med grant to my colleague, Michael Rawlins, as principal. The EEC does have some virtues, after all.

Data examined risks by dose for five commonly used nonsteroidals and acetaminophen with separation into lower, middle and high dose bands, using logistic regression, adjusting for aspirin, anticoagulants, smoking and GI history, but significant effects for alcohol were not found and, therefore, not adjusted for.

The first panel summarizes case characteristics. Note that British subjects were all

age 60 and over, and that Swedish studies excluded those with prior UGI complaints. Others did not.

The second panel shows overall ulcerous shares with 95 percent confidence intervals for acetaminophen, ibuprofen, diclofenac, indomethacin and piroxicam with, off the scale on the right-hand side, ketoprofen. The last was not considered further, as case numbers were too small for dose division.

The next panel shows ratios by dose for the three drugs with the lowest recorded figures. Actual point estimates for ratios were as follows: For acetaminophen, 1.2, 1.2, and 1.0, at lower, middle and upper doses; diclofenac, 2, 3.2 and 12.2; ibuprofen, 1.1, 1.8 and 4.6.

The next panel shows figures for indomethacin, 3.2, 6.8, and 20.4; naproxen, 4.8, 5.4, and 15.6; and piroxicam, 9, 12.0, and 79.0, going off the scale again.

The remaining panel sets out all this data for the six together. It's not changed in any way. It's just put together. Note confidence intervals a tighter stress, acetaminophen at all doses, and for lower dose, under 1200 milligram daily, ibuprofen, all with point estimates close to 1.0.

Note also that 80 percent of ibuprofen data were obtained in the United Kingdom, this

deriving from individuals aged 60 and over with a recorded frequency of 40 percent of upper gastral and intestinal complaints.

The data presented here seem entirely compatible with the large scale clinical trial results obtained in France in studying TO analgesic use. They contrast, to some extent, with the ACG study, also referred to earlier. However, that study has some problematic design features which seem to me to limit its generalizability.

I conclude that judicious choices of drug and dose could materially reduce or completely eliminate the risk of upper GI complications due to NSAIDs when in OTC use. Thank you very much.

DR. MOORE: Okay. So I am Nicholas Moore. I am in Bordeaux, a clinical pharmacologist. I have worked with Boos, Navartis, Roche, Synophe, Aventis, Healthsyn, Merck, Monsanto, Pharmacia, Pfizer and UCB on ibuprofen, ketoprofen, naproxen, diclofenac, and presumably on others, preferably at low dose, looking at the risks of low dose and specialized in the assessment of drug risks; and I have been doing that work for the last 20 years.

I have worked on clinical trials of these low dose analgesics at OTC doses, and I have included more than -- done 13,000 patients in these studies.

Since everything has been said on all the rest, I have concentrated on renal failure and the risk of renal failure with those and, of course -- excuse me -- my travel is taken care of by the International Ibuprofen Foundation which is financed by all the companies that make ibuprofen. So it's indirect interest.

I have concentrated on the renal failure, because the GI has already been entirely seen. We know that there is a pharmacological basis for renal failure with nonsteroidals. COX-2 is fundamental for the maintenance of glomerular filtration rates, and when this is stimulated, for example, in people at risk with hypobulemia, the elder and children, patients with heart failure, etcetera, etcetera, we know that this causes a much higher risk of renal failure, and this is true for all NSAIDs, and there have been case series or case reports for every single NSAID, including ibuprofen.

Therefore, the question of the risk of widespread OTC use and renal failure is a perfectly valid question. I have tried to see whether there was any kind of risk.

Now in this pain study which we have been discussing and which you have heard of already, 9,000 patients almost treated for OTC indication, there was

less than .1 percent, .2 percent of any kind of urinary symptoms. There was not a single case of clinically identified renal failure.

There was, as was shown earlier, the same rates of GI events with ibuprofen and paracetamol. if you look in the elderly, and this is the data that Mary Griffin showed earlier, I just want to show you that what we are looking at is -- I'm not quite sure why that thing became an upside question mark. Oh, yeah, this is a PC. Okay. Anyhow, odds ration in this population is one. So that the ones we are interested in, which is the OTC use, there is no additional risk in the elderly.

This is not true for the higher doses, and we know this, and this was expected. But at the very low doses, like for the GI bleeds, there is no risk associated with the use of ibuprofen less than 1200 milligrams per day.

If you look at children, for some strange reason nobody has talked about Lesko's marvelous clinical trial, randomized, double blind clinical trial, 84,000 children. I don't think you can get anything much bigger than that, and he looked at hospitalizations for serious events, GI bleeds, renal failure.

Okay. No difference in GI bleeds in

children between acetaminophen and two different doses. I'm sorry, it's 5 and 10 milligram kilo, not 10 and 15. No difference between ibuprofen and paracetamol, and there was not one single renal failure. This is in about 50,000 children treated by ibuprofen at OTC doses for fever, including 27,000 children of less than two years of age.

Also, he looked at the admission creatinine, BUN, in children who were hospitalized for any kind of reason, including dehydration, including fever, and there was no difference between the paracetamol and the ibuprofen groups. So that this does not seem to be an issue collectively for these patients.

In newborns there was a recent meta-analysis of all the studies done for -- compared with indomethacin. The efficacy was the same as indomethacin. There was no renal toxicity noted in any of those studies of newborns, which are a very high risk group.

Finally, in overdose, if you look at the problems -- this has already been said before -- there is no need to monitor renal function if the intoxication is less than 6 grams per day, and there is -- for intoxications up to 60 grams per day, there have been instances of renal failure. They have all

been reversible, and I would just like to note that there is not one single published case of single constituent fatal ibuprofen overdose.

To come back to a number of points, since I still have one more second, there is one point which should be noted. When you double or triple the dose of ibuprofen from 1200 to 2400 or 3600, you are just going to the mid-part of the prescription doses of what is still the best tolerated prescription NSAID. If you double or triple the daily dose of paracetamol -- excuse me, acetaminophen or aspirin, the situation is very, very different.

Thank you for your attention.

CHAIRMAN CANTILENA: Thank you, Dr. Moore. We now have an opportunity to ask questions of Dr. Topol, Langman and Moore, and I guess I'll ask Dr. Wood if he has any questions.

DR. WOOD: Yes, I have a question for Eric. I mean, if I understand what you are saying, you are saying that your acknowledge that the 350 milligram dose of aspirin produces GI bleeds.

DR. TOPOL: 325?

DR. WOOD: 325, right, yes. And that the lower doses do not. But --

DR. TOPOL: Well, they do less.

DR. WOOD: Right, but I was sort of

confused. The dose -- The adult dose over-the-counter is the 325 dose, which is the issue we are debating here.

DR. TOPOL: Well, but actually, that's part of the issue, is that --

DR. WOOD: Well, let me finish the question.

DR. TOPOL: Sure.

DR. WOOD: So is it your position that that dose should be reduced?

DR. TOPOL: Yes.

DR. WOOD: Even for pain?

DR. TOPOL: Well, no. This is just for cardio-protective indication. I think you bring up the central point, Alistair, of course, that at Cleveland Clinic we have had to contact thousands of patients now to reduce their dose, which had customarily been 325 milligrams per day, based on these recent data.

Until new data become available, we review this as an important reference set, and it does strongly suggest about the bleeding dose dependency when one goes up from 160 to 325. So we have advised our patients, based on these new findings and, of course, the meta-analysis, because obviously, it is very important that you could reduce bleeding, but

would you compromise efficacy? There is no sign of that whatsoever, in fact. If anything, it's possible that the lower doses could be -- enhance efficacy.

So based on that, we have indeed gone to the 81 to 162 milligram recommendation and, of course, that is available over-the-counter.

DR. WOOD: Just to extend the point, the subject of our discussion today, the take-home message I take from that, in contrast to most of the other presentations, is that the 325 milligram dose is associated with an increase in bleeding and that that currently is not well addressed in the labeling. Is that fair?

DR. TOPOL: That's right. The only indication for the 325 milligrams, as Dr. Hennekens did point out, is it's been nicely shown in the acute phase, for after the first dose in the hospitalization. But outside for chronic dosing, that would not be what we would recommend. We would recommend to drop down to 81 or 162 milligrams.

CHAIRMAN CANTILENA: Okay. Dr. Neill?

DR. NEILL: The current labeling for aspirin tells patients see your doctor before taking this product for your heart or other new uses for aspiring, because serious side effects could occur.

When they call me and come in to see me

and I tell them go to the drugstore, buy this bottle and take it, they are going to take home a package which does not include risk information about the long term use. So they will have to remember what I've told them in the office and base their decision about whether to continue this medicine on what I tell them in the office.

I've been trying to think about other medicines for which that's the case which I may prescribe for a prescribed indication, not an OTC indication, and for which there is a medicine that they are going to pick up off the shelf. Now Prilosec or some of these other medicines that we have discussed at this committee before may become one of those, but we are not going to talk about those today.

Should aspirin be subject to the same kinds of prescribing information requirements that other prescription indication medicines are subject to or not?

DR. TOPOL: Well, that's certainly, I guess, perhaps a point for debate. But as already mentioned earlier this morning, we have a big problem in the patients who need to take aspirin, who fulfill all the criteria for secondary or primary prevention. There is a woefully inadequate number of those patients already today who are not getting the

protection.

So anything that would restrict that, of course, would be considered problematic. On the other hand, we are continually getting new and important data, I believe, about the aspirin and the appropriate dosing, and that, hopefully, can get somehow communicated, and the appropriate dosing to maximize the safety and efficacy would be the ideal strategy in the maximum patients who, of course, fulfill criteria for benefit.

CHAIRMAN CANTILENA: Yes, does Dr. Hennekens have a comment?

DR. HENNEKENS: Yes. I wanted to speak on behalf of the anti-platelet trials collaboration, in full agreement with Eric's recommendations about 81 milligrams being the optimal dose in the nonacute phase, and 325 in the acute phase.

Our belief is based on the fact, as he suggested, that the benefits seem similar across the wide range of doses from 75 and above, and there does seem to be this dose dependent increase in side effects.

Having said that, with respect to the specifics of the labeling on GI bleeding, I did want to point out that in clinical trials that compare directly aspirin with control, the proportional

increase in the risk of a major extracranial bleed was similar across the range of doses from 325 to 75. They were specifically 1.7 for less than 75, 1.5 for 75 to 150, and 1.6 for 160 to 325, and in addition there were two trials that directly compared 75 to 325 doses with less than 75 doses and found no significant difference in major extracranial bleeding.

So we do agree with the conclusions. We do agree with the side effects in general. I think the issue that we might disagree with might be about whether there is at this range of dose the dose dependent increase in bleeding.

CHAIRMAN CANTILENA: Dr. Cryer?

DR. CRYER: Yes. My question is directed to Dr. Moore. I was previously going to ask it of Dr. Sica as it relates to the renal effects of ibuprofen. So you can strike my request for the earlier question.

It really gets to this issue of what is currently in the label for ask your doctor if you have a history of hypertension prior to taking this product. I'm trying to get a sense of where the data are that support that recommendation within the label with respect to the hypertensive effects of OTC doses of ibuprofen.

So from your experience or from your

reviews, do you have any -- Can you provide us any insight about that?

DR. MOORE: That's a very complex question. The data on the inhibition of the anti-hypertensive effect, especially of diuretics, comes from interactions with full dose classical NSAIDs, and I think it has been adjusted to the OTC dosages, but I'm not sure I have seen any study of the interaction of ibuprofen low dose, OTC doses, with anti-hypertensive treatments that did show that there was interaction.

By prudence, I would keep that. I would also keep -- because in the pain study we've seen there is very clear dose relationship between the number of concomitant medication and the adverse events, the more medication you have, the more adverse events you have is true for all three drugs. I would be very, very -- I would very strongly support that people that have chronic diseases, please talk to their doctor or to the pharmacist before taking this kind of drug as a matter of principle.

That was the major risk factor for adverse events, more than age.

DR. SICA: I can add something to that for you. Just having recently reviewed that, there is virtually no data on the OTC use on that. It's a

complex amalgam of data, and it's probably not a precise judgment to take prescription strength doses and walk back to OTC doses to presume it has the same presser effect to increase blood pressure, particularly the short pulse therapy as occurs with OTC therapy.

It's believed to be an attenuation of diuretic effect, more so for loops than for thiozides, and thiozides are much more commonly used in hypertension therapy than is the case for loop diuretics, and it's also the chronicity of therapy and the underlying subset analysis of what type of hypertension that you have. But for the short term use, there is very little impact, at least I would imagine, to occur with this, if it was to be studied in some sort of meaningful way.

CHAIRMAN CANTILENA: Okay, thank you. Final question from Dr. Brass.

DR. BRASS: Yes, thank you. It's more of a comment. I just want to reiterate my perspective, that we are seeing an awful lot of mean population data, and I do not believe that is the issue. We all know, I think, and believe that in general populations these drugs are very, very safe.

The issue, I think, is whether or not there are subgroups of the population which require

special attention and special warning, and those are not identified by these types of studies. To the degree they are, all the information is in the outliers, not in the point estimate of the mean response.

So that a rhetorical question for Dr. Moore would be how many patients over the age of 65 with a baseline creatinine of 3 on corticosteroids were included in the cohort? And we are going to be faced with again extrapolating data about mechanism of action in smaller studies, and I don't think we should be falsely reassured about those cohorts from the general populations.

DR. MOORE: If I may --

CHAIRMAN CANTILENA: If you happen to know the answer, Dr. Moore, go ahead.

DR. MOORE: Very rapidly, the number of users from the Medicaid data, I think, you should ask Mary Griffin. Those over 65 with steroids. Normally, steroids -- we didn't have any in the pain study, but I think there are two populations here we are talking about.

One is the usual OTC guy with pain, buys the stuff, takes it for three days, and that guy is not at risk. Then there is the chronic use of "prescription" type usage in OA and RA that have been

using these drugs for years and will go on using them for years, and those should normally be "prescription" type use. That is the population at risk.

Three percent of the users represent more than 40 percent of the patient time at risk, if you look at OA users -- at RA users. And the risk for common pain and everyday toothache is just about nil. I think this is what you want to identify.

CHAIRMAN CANTILENA: Okay, thank you very much. We will now conclude the morning session. We will adjourn for lunch and return back at 1:30.

(Whereupon, the foregoing matter went off the record at 12:30 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:37 p.m.)

CHAIRMAN CANTILENA: The plan for the afternoon is we'll start with -- if there are any questions that were not answered. I would ask the panel to be very specific with your questions, if you are going to be asking either the FDA or the sponsor. So try to be very specific.

We will start with that, the unanswered questions from the presenters, and then after that we will go into -- Basically, as you look at your sheets, we will go into Question 1, and we will specifically discuss GI, and then we will go through the questions for GI.

So my plan is to, as I said, follow up with the questions, then open a general discussion of relative risk for consumers at the maximum dose, and then to go then to 1(a) and 1(b) for GI and question 2(a), again sticking with GI, and then we'll come back and have a general discussion for kidney, talk about the issues there with subpopulations and risk, and we will do -- So that's basically questions 1(a) and (b) for kidney. Then we will do question 2(b) which focuses on kidney. Then we should be able to proceed with 3, 4 and 5 as advertised.

so let's start with questions that were

left unanswered from the session this morning, open it up for general. Dr. Brass and Dr. Laine.

DR. BRASS: Again, as I think about the problems we are going to be talking about this afternoon, I kind of divide them into two categories. One are problems associated with use as directed by the label, which I think is a subgroup question and, two, where the issues relate to consumers who do not follow the label.

I'd like to explore the issues of subgroups, and in particular groups at risk for short term adverse consequences from renal effects. I tend to believe that small increase in blood pressure, even in the hypertensive, for a few days is probably not a terrible risk, but I'm a little bit more concerned about the individual with underlying heart failure who a few days of decreased GFR and fluid retention may be the difference between compensated and decompensated symptomatology.

Would somebody from any of the sponsors like to comment about the perception of that risk and the need to avoid unsupervised use of these medications in patients with symptomatic congestive heart failure?

CHAIRMAN CANTILENA: Okay, Dr. Sica?

DR. SICA: I'll take it from, hopefully, a

practical point of view. I think what you describe is something I view as an issue, but it is a compromised population. We look at some of the Dutch data and other such data. NSAID use is a cause of deterioration and a cause for increase in heart failure and admissions to the hospital.

The mechanisms are a little bit dicey right now, one of which may be an intrinsicability to block salt water handling of a natural nature which is already compromised because of CHF. Second, there is a blunting effect of diuretic action which is not kinetic, because both are truly secreted, but it appears to be pharmacodynamic at the thick ascending limb.

I think, if it's a compromised population, we have to use the same caution -- precautions as always. You raised an interesting point in that, if you've got someone with subclinical congestive heart failure who has not yet been so diagnosed by a treating physician, that's less of a problem there. But those under therapy, I think the guidelines that are there classify them as at risk already and have to be talking to a physician.

DR. BRASS: So you agree that a label directed toward deselection of patients with a congestive heart failure would be an appropriate

component of the label?

DR. SICA: I think heart failure should be a compromised condition like the others, and that any good physician who is treating a heart patient should advise their patient already ahead of time about the cautious use. The patient shouldn't have to find that out after the fact. That is part of heart failure management, as I view it, though.

CHAIRMAN CANTILENA: Okay, a comment from Dr. Berlin.

DR. BERLIN: Okay, thank you. I just wanted to provide some additional data. I did over lunch pull some of the studies that have been done on the effects of low dose ibuprofen in terms of antihypertensive effect for people who are being treated.

I think the vast majority of studies demonstrate no effects. So I think that's an important context again as we are talking about any of these underlying conditions. I think we have to factor in the magnitude of any effect.

Second is that, as I pointed out earlier this morning, there is a specific warning which says, if you have any continuing medical condition or you are being treated with any continuing medication -- and I think this is going to be a topic for your

further consideration about specificity versus generalities and how many specifics you can put in and whether that achieves more than being more general.

So in terms of the data, I think the low doses appear to have minimal effect, at least as measured on blood pressure. As far as the specific language, I think there are counterbalancing arguments, and there already is language.

Just a final point is that two-thirds of the people who use the product already consult with their physician or have consulted with their physician.\

CHAIRMAN CANTILENA: Thank you. Dr. Laine.

DR. LAINE: For the agency, we have only been given the aspirin 325 milligrams, since probably a large proportion of people use aspirin 81 or 325 for cardiovascular, and I know that has professional labeling and approval, Is there a -- Can we see an 81 milligram and a 325 for cardiovascular? It's not approved for consumers for cardiovascular. Is that correct?

DR. GANLEY: That's correct. In Volume I, I think it's subsection F, has the complete labeling. It's essentially like a prescription label, the way it's written. You know, it's not consumer friendly.

So I think we have some of the specific toxicities related to GI that are included in that on a slide, if you are interested in that, but it's virtually impossible, I think, to --

CHAIRMAN CANTILENA: Charley, we also have a copy here that we can hand out to the members.

DR. GANLEY: It's in Volume I of the FDA background, if you have it there, Section F. It's in the large pile there.

CHAIRMAN CANTILENA: Yes. It was hidden, I think, in the *Federal Register* section. It's actually in the *Federal Register* which I think some of you may not have read every word in that volume.

DR. GANLEY; It is Section F there.

CHAIRMAN CANTILENA: You will be appropriately docked in your compensation. Anyway, we can hand out this, which I think is a little easier to read.

DR. GANLEY: It's not slide friendly. Let me put it that way.

DR. LAINE: That's fine.

CHAIRMAN CANTILENA: Okay. Was there a question over here from Dr. Griffin?

DR. GRIFFIN: I was just wondering how comfortable the sponsors feel about sort of abrogating their responsibility for informing consumers to

referring them to physicians who may or may not educate their patients appropriately.

We have a lot of evidence that physicians co-prescribe corticosteroids and NSAIDs. They co-prescribe coumadin, anticoagulants and NSAIDs. They give NSAIDs to people in congestive heart failure, and that even if they are -- now that there are recommendations out as far as NSAID prophylaxis for high risk groups, people continue to prescribe NSAIDs to very high risk people without prophylaxis.

So I think that it's a little bit paternal to sort of say, well, if you have these conditions, talk to your physician. I think it's also not very effective oftentimes. Physicians have a lot of things that they do with patients, a lot of objectives, and they don't always do a good job.

So to my mind, I think the sponsors have a responsibility to inform patients about the risks of the drugs directly.

CHAIRMAN CANTILENA: Okay. Dr. Cohen and then Katz.

DR. COHEN: I suppose this could be for Wyeth, since it's about the ibuprofen, the proposed label on ibuprofen. I just want to read one of the statements. This is in regard to drug allergy. It says: Do not use if you have ever had an allergic

reaction to any other pain reliever, fever reducer.

We heard this morning that people are not familiar with the drug category necessarily on these products, NSAIDs, aspirin, etcetera. I wanted to know how much is known about cross-allergenicity between aspirin and the nonsteroidals and then nonsteroidals and aspirin, and whether or not the word aspirin should be there, and vice versa on the other products, to make it clearer.

CHAIRMAN CANTILENA: Okay. Dr. Berlin?

DR. BERLIN: That was language that was specifically put in there at the request of the FDA during the negotiations for the NDA approval, and there have been some modifications since. So I can't give you the exact rationale.

There is cross-reactivity which, in fact, involves all of the analgesics, actually, to some extent or another.

DR. COHEN: Any information on the prevalence?

DR. BERLIN: I don't have those numbers.

CHAIRMAN CANTILENA: Thank you. Dr. Katz, and then Dr. Cush.

DR. BRASS: If I could just address the question, because I think part of this relates to the aspirin sensitivity syndrome. That's the class NSAID,

and which consumers understand as an allergy. I think that the blanket warning, my recollection was, was oriented toward that specific syndrome, not the other types of hypersensitivity that might be associated with the individual agents, and that's why it has the broad language in there, and trying to make it in the consumers' language, because they wouldn't understand aspirin hypersensitivity syndrome.

CHAIRMAN CANTILENA: Thank you. Dr. Katz, Cush, then Rumack.

DR. KATZ: My question is about efficacy. It's sort of -- I come at this from a pain management point of view, and it's very easy to say, well, you know, if someone is on 200 milligrams of ibuprofen and that's safe, well, our job is done and we can go home. But that may represent important under-management of pain.

So my question for the sponsor is: Are there actually any clinical trials that show that a 200 milligram dose of ibuprofen is efficacious for any type of pain other than dental pain, and I wonder if somebody could give a specific answer to that?

DR. COOPER: Yes. I'm Dr. Cooper from Wyeth Health Care. In our background document, we have a whole section on efficacy, and we showed data across almost every type of pain, headache, sore

throat, muscle aches and pains, migraine headache, dental pain, dysmenorrhea, arthritis. Two hundred milligrams is at least as effective as 1,000 milligrams of acetaminophen, and 400 milligrams is consistently more effective in many of those types of pain.

The more severe the pain, the more effective the ibuprofen looks relative to acetaminophen, and that's one of the real benefits of ibuprofen, and you shouldn't forget that in the benefit to risk. It is truly a more effective analgesic than acetaminophen.

DR. KATZ: And what is the maximal efficacious dose of ibuprofen in those single dose studies?

DR. COOPER: Four hundred milligrams.

DR. KATZ: And more than that doesn't provide any additional efficacy?

DR. COOPER: That's correct. There is also some information in that background document that shows above 400 milligrams, you reach a plateau dosage for peak effect. You might extend the duration of effect slightly, but you don't gain enough benefit to use a higher dose for analgesia.

For arthritis for an anti-inflammatory effect, you do use higher doses.

DR. KATZ: Thank you.

CHAIRMAN CANTILENA: Dr. Cush.

DR. CUSH: Mine is not a question but rather a statement. This morning we heard a few statements, one that the current labeling is adequate. We heard that the vast majority of the uses is within conformance of label instructions. We even heard numbers with regard to actual numbers as far as use or less than maximal use for drugs such as ibuprofen.

I think that is very optimistic, and I think most of us share that optimism as far as efficacy and the safety of these drugs. However, it should be noted that this less than maximal use or within prescribing guidelines use by most patients is not due to discussions with physicians.

I think some of it might be, but the vast majority of my patients who are taking OTC products at my direction are taking less than what I prescribe, usually 50 percent of what I prescribe. Moreover, it is not due to them reading the labels.

We heard yesterday and today from both the National Consumer League and the American Pharmaceutical Association that patients don't read labels adequately, don't know the names of the medicines they are taking, and basically it's gestalt when they can use medicines.

I think this is largely due to patients' belief that they can -- or that they are basically medicine minimalists or -- and that's sort of good from a safety standpoint -- or the more worrisome belief that they have enough -- an adequate information that they can self-prescribe. It's that latter belief that gets us sometimes into trouble, that we are worried about.

Hence, I think that we should, you know, congratulate ourselves as optimists, but also we should be sort of thinking about worst case scenarios when we are considering our revision of labels. I think that we should revise labels in an organ-specific manner. I think that we need to mention in there some of that concerns that we have, including the risks for some of the problems that have been identified.

I think, again, we hear today, as we heard yesterday, that packaging continues to be a major impediment to safety, that the more information that you put on packaging, the less likely patients are to read it. It's sort of looking at a contract written by a lawyer. The longer it is, the less likely someone is to read it. The shorter it is, the more they might actually try to struggle at reading it and trying to understand it.

So I think we should have minimal parts of the packaging which are devoted to minimal wording in bolder type that has the name of the drug, has the indications for the drug, says do not use with other things, and call your doctor if you use it chronically.

CHAIRMAN CANTILENA: Okay. Thank you for the statement, but if others can sort of confine their questions to specific issues for sponsors and the FDA, and then we will sort of head into the general discussion. Next, Dr. Rumack, then Alfano.

DR. RUMACK: I'm a little bit unclear on the issue regarding prescription indications for aspirin and over-the-counter indications for aspirin and the issue with -- In the last couple of years there have been data to show that apparently, if you take aspirin for cardiovascular effect and then you follow it with ibuprofen, that you diminish that effect.

I was unclear on whether we have come to any conclusions on the safety of taking both of those agents at the same time, if that should be addressed on a label.

CHAIRMAN CANTILENA: So you have a question for the sponsor about that or is that something you want to talk about later as a group?

DR. RUMACK; Well, I'd like -- There are two questions there. One was for the FDA. Still, I'm not sure that I understand the prescription versus nonprescription labeling on aspirin. I understand that cardiovascular must be prescription, although it seems to me, when you look at the box, that people -- it says for cardiac care or something, for your heart, and so I didn't understand where that was.

The second really is for the sponsor. That is if you take both of them together, where does that end up both for the heart and --

CHAIRMAN CANTILENA: Okay. I think, actually, that's sort of the first part we are actually going to handle under Item 3 later when we'll talk about that in the labeling. Then I guess we can frame the second part as a question for sort of what are the safety implications for adding on a second nonsteroidal, if you are on that aspirin for cardiovascular.

Do any of the sponsors want to comment on that? Go ahead, Dr. Hennekens.

DR. HENNEKENS: I believe your comment stems from a *New England Journal of Medicine* paper by Gareth Fitzgerald and co-workers where he did a randomized, double blind crossover study. It was true in that small randomized trial that, if you pretreated

with ibuprofen, then basically that would inhibit the beneficial effects of aspirin, whereas, pretreating with aspirin did not inhibit any beneficial effects of ibuprofen.

There were no issues about concerns about side effects. I think the big issue about that study is whether or not it has any clinical relevance. On the assumption it has clinical relevance, I think the clinical pearl is that, if one is taking both drugs, take the aspirin at least two hours before the nonsteroidal, but that's based on very limited data whose clinical relevance, in my view, is still not clear. But I don't think it's a concern about side effects. It's a concern about efficacy.

DR. LAINE: I would agree about the lack of clinical relevance being shown, but that misstates the paper a little, because they did a second part of that study showing, if you took the ibuprofen chronically for a week, whether you want to call that chronically for six days, even if you didn't take it -- you know, it wasn't that you had to take the ibuprofen just before the aspirin. Even if you took the aspirin before the next dose of ibuprofen, so eight hours after the previous dose of ibuprofen, you still had almost complete lack of the antiplatelet effect of the aspirin.

So again, nobody knows the clinical relevance of that, but that suggestion in the second part of the study would say that it's possible, if you were on regular three times a day ibuprofen at higher doses than over-the-counter, I might add, that it would potentially interfere with the cardio-protective effect of aspirin. But again, not clinically documented.

DR. HENNEKENS: I agree with you completely. I would put it in the realm of a research question rather than a clinical or policy question.

CHAIRMAN CANTILENA: Okay, thank you. Dr. Alfano.

DR. ALFANO: Yes. This is a question for Dr. Langman. You presented data on the relative risk for a bleed, GI bleed for ibuprofen, which was slightly over one. In the FDA documents from earlier in the day, there is a study reference which shows, at a similar dose, that it's actually a risk of three. What's the difference in the database?

DR. LANGMAN: Thank you. I think you are referring to the Blossom-Matroughan study of over-the-counter drug use referred to as the ACG study. Is that correct?

DR. ALFANO: Correct.

DR. LANGMAN: There are one or two

features of that study that make me a little bit wary about accepting it at face value. Firstly, the cases and controls were, I think, volunteered by gastroenterologists in sets of ten each, but if you look at the data there are actually 627 cases and 590 controls, which argues for a lack of balance from somewhere, which shouldn't be there.

The cases, 45 percent are aged 65-plus, but only 33 percent of the controls. That is quite a substantial difference in the area in which you are working.

Secondly, 62 percent of the cases are male, but only 49 percent of the controls, despite the fact that they are older where you would expect them to be more women than men. There are also differences in the proportions of bleeding in controls and cases which are hard to understand, and the alter ratio for the low dose of ibuprofen, the confidence interval goes below one anyway.

Now if you take all that and stir well, you say I have reservations and, if you read the paper, they themselves say that they have reservations. They do not regard it as definitive and, in essence, they regard it as explorative.

So I think you've got a warning label attached to it by the authors and by the data.

CHAIRMAN CANTILENA: Okay, thank you. Are there any further questions to the presenters, either FDA or the sponsors? Okay. Let's move on to point 1(a), to describe the relative risk of gastrointestinal bleeding for consumers using the maximum recommended daily OTC dose of NSAIDs or aspirin.

What I'd like to do is actually focus again on just GI and open the discussion to talk about what we've heard and what we've read and what we know. Perhaps I can ask Dr. Cryer if he would like to sort of start the discussion.

DR. CRYER: Well, this discussion in part continues the comments that Dr. Langman just had, but I will -- To continue those, I would say that when we have this discussion, I think we really need again, as I suggested earlier this morning, to separate this issue from aspirin and the nonaspirin NSAIDs, because I think they really do behave differently.

With respect to the nonaspirin NSAIDs, really, the bulk of the data is really a discussion of low dose ibuprofen. I would say that there are some concerns about the data. None of the datasets are perfect, but it looks as if the relative risk is going to range somewhere between slightly greater than one up to three, so somewhere in that range.

So given the discussions about where, in fact, it falls within the range -- Well, I should also say that I agree very clearly. I didn't state it, but it was stated several times this morning by sponsors that, of the nonaspirin NSAIDs, ibuprofen probably has an ulcerogenicity which is less than that associated with naproxen and ketoprofen, and that was demonstrated to us by Dr. Langman.

So one consideration with respect to labeling is, well, I would guess that the OTC labeling for those three products would be similar. So to which of those products do we associate a relative risk, given that they are ulcerogenic effects are different. They differ.

So are we going to have this discussion with relative risk related to naproxen, ketoprofen, ibuprofen? I mean, it's all over the board. But with specific regard to ibuprofen and its relative risk, I currently think the risks as they are stated in the proposed label are probably -- There are some minor modifications, but at least in general terms, they seem to be more or less within the realm, I think, of how it should be reflected to a consumer.

CHAIRMAN CANTILENA: So your point with ibuprofen is it is significantly less, but not zero or it is zero?

DR. CRYER: I would disagree with the contention that it is zero.

CHAIRMAN CANTILENA: Okay. Could you comment on aspirin?

DR. CRYER: Aspirin is problematic, and I think this really is going to overlap into the discussion that we will have, I guess, in question number 3 about this issue of professional labeling, because I, too, am still a little bit unclear as to how its indications are described to consumers and to patients; because -- I mean, and to physicians.

Clearly, the majority of its use, I think -- I would agree with the use of aspirin for cardiovascular prophylaxis, and so that discussion then becomes, well, is there risk associated with those low doses of aspirin? Probably yes, but the cases -- I think we have all agreed that the benefits far exceed the risks.

Again, as it relates to low doses of aspirin, if that's what we are going to be describing in the drug facts or on the label, then my sense is that the risk is increased, but that increased risk is more or less appropriately described in what is proposed here as it relates to low daily doses of aspirin, 325 milligrams or less.

Now if we move this discussion to higher

doses that might be used as analgesics or for anti-inflammatory effect, I think that risk needs to be stated in a different fashion, because I think the data are fairly clear. The risk significantly increases.

So it really depends on what dose and for what indication.

CHAIRMAN CANTILENA: Fine. Thank you very much. Other comments on the relative risk issues for gastrointestinal bleeding? Dr. Johnson?

DR. JOHNSON; My question is not exactly on relative risk, and this, I think, would be for either Dr. Cryer or Dr. Griffin. That is, Dr. Griffin presented some absolute risk data, which I think in some ways is more useful in this discussion, for those over 65.

So my question is: The relative risk is somewhere in the one to three range, but what is the absolute risk in the less than 65 group which, based on the data from at least one company, is the majority of users of at least ibuprofen? Do you have data on that?

DR. CRYER: To get to that -- I mean, I think there was one that I reviewed for you that looked at specifically OTC users within the last 30 days, questioned them about their use and questioned

them about their side effects within that experience.

The absolute risk for a GI bleed or an ulcer with an OTC user was 0.6 percent, but although that seems relatively low, I think we need to put that into the context of the expansive use of these products in an OTC fashion.

So the absolute effect across a population, while on a percentage basis is seemingly small, is likely to have a considerable impact. That 0.6 percent, at least in that experience, was a -- when compared to the absolute risk in the placebo risk, gave a relative risk of 2.

That also did not indicate for which of the OTC products that absolute risk applied or whether it was a combination of the products. So I can't say for which drug we are specifically talking about in that specific experience that actually gave us absolute risk in an OTC population over the short term.

CHAIRMAN CANTILENA: Dr. Wood.

DR. WOOD: Yes. I like to think about it in terms of, if we are going to introduce some labeling changes, can we introduce labeling changes that will make an impact?

It seems to me that informing people that they are at increased risk if they are taking

corticosteroids, if they are taking Warfarin, and perhaps -- and informing them, if they are elderly -- although I can tell you there isn't much we can do about that. We are kind of stuck with being elderly -- and also informing them that there is an increased risk if they are taking other nonsteroidals seems to be a worth goal.

All of that presupposes, I guess, that there's some generic warning that precedes these statements, that says that these drugs cause an increased risk of GI hemorrhage and that the following groups are at particular risk, and you need to think more carefully, or whatever wording we want to use in there.

I'm not all that enamored with the idea of calling your physician. I'm not sure that that helps very much, and Marie already addressed that. So I think, as we go through the process, it's worth addressing labeling changes form a perspective of have we a reasonable level of confidence that whatever changes we introduce will have a likelihood of reducing risk for patients, and rather than just sort of laying stuff out there and hoping that that makes us all feel better.

CHAIRMAN CANTILENA: Okay. So, actually, if I can ask: When we talk about relative risk for GI

bleeding, does it make sense, or is everyone comfortable with the idea of segregating out the aspirin versus the nonaspirin? Is that something that helps you sort of think about relative risk, and is that something that we should sort of use as an underpinning, I think, for our discussions? Yes, Dr. Laine?

DR. LAINE; I'm not sure -- I mean, I would agree exactly with what Byron talked about, but I'm not sure it matters, and I wonder whether we should get stuck on relative risk. You know, lots of studies will give slightly different relative risks, and none are wrong. I mean, you really have to get the general gestalt of its increase.

I mean, especially for the consumer, I'm not sure why we need to worry whether it's a twofold or threefold increase. We know what the baseline is. We know that it's probably increased to some degree. Whether it's 1.5 increased or 3, I'm not sure it really matters in terms of our determining a label, at least from my point of view, especially because all we are going to do is fairly simple wording. We are not going to be giving a lot of information.

So my view is, although I agree with what Byron talked about, I'm not sure it's going to change how we suggest a label.

DR. CRYER: I'm in agreement as well. I would say that aspirin, when used at the doses that the population is likely to -- for those indications, low dose aspirin, the absolutely risk is probably comparable to what we are seeing with the OTC NSAIDs or within the same ballpark that I don't think it needs to be distinguished as it relates to labeling, the information that is given to a consumer.

I do very much agree with the point that Dr. Wood made, that it really should be stated up front very clearly to the consumer that the class of these products places one at increased risk for ulcer bleeding.

CHAIRMAN CANTILENA: Okay, does anyone have any other comments about this particular topic? If not -- Oh, I'm sorry. Dr. Cush.

DR. CUSH: What about adding the line that Byron had in one of his slides, which is basically that risk appears -- the risk appears to rise with increased use, meaning number of tablets, length of use?

CHAIRMAN CANTILENA: Okay, yes. That could be something that we talk about when we get to the label in just a few minutes, but your point that there's a dose response, I think, is well taken.

All right, any other comments about

relative risk? If not, we'll charge ahead and look at item 1(b), again now just focusing on GI. I guess we will do this as a -- Well, first of all, does anyone in the group feel that they would be helped by a discussion concerning subpopulations and how that would impact on how they would answer the question or are they ready to sort of address the question of are there subpopulations who are at greater risk?

Is there anyone on the committee who feels the need for expertise of their colleagues on this? Dr. Crawford, do you have a specific question or topic?

DR. CRAWFORD: No. Perhaps Dr. Cryer or another member, if you would just give a summary of those major subpopulations so that we could frame our thought process.

CHAIRMAN CANTILENA: Dr. Cryer, you are probably never going to agree to make a presentation at the committee again. We are picking on you, but if you wouldn't mind.

DR. CRYER: Sure. So the older age group, likely those people who are greater than age 65; the concomitant use, as we learned from Dr. Griffin's presentation, of corticosteroids or, in particular, anticoagulants; a previous history of ulcer disease, especially a previous history of complicated ulcer

disease would be the most common risk factors that we -- oh, and then the other one that really needs to be -- and thank you, Dr. Laine -- that absolutely needs to be, I think, in my opinion, reflected in some way on a label is this issue of multiple combinations of NSAID use. That really is a public health concern that we need to educate the consumer on.

CHAIRMAN CANTILENA: Thank you very much. So let's -- I think we can do this fairly quickly with sort of that as our --

DR. BRASS: I have a follow-up question.

CHAIRMAN CANTILENA: Go ahead.

DR. BRASS: Actually, that matches exactly my five list, but I have a question mark next to one of them, and that's the elderly; because I understand it's a risk, but I have no idea what to do about it.

Do you say that you can't use it if you are old or -- and that's why I earlier asked about whether there's differential data on pharmacodynamics. For example, is there any basis that a lower dose might be recommended if you are elderly to get equivalent efficacy and reestablish some risk to benefit?

I agree with the category, but I'm quite confused as to how to deal with the elderly component.

CHAIRMAN CANTILENA: There's actually only

one of the compounds that I know of which has altered pharmacokinetics, and there was a change in the label in the elderly. But are there other examples? Dr. Katz?

DR. KATZ: Well, I was interested in pharmacodynamics, actually.

CHAIRMAN CANTILENA: Well, actually, how that actually came to be was -- I think it was for the over-the-counter switch for naproxen where you actually saw a change in the pharmacodynamics, which we then figured out was as a result of the pharmacokinetics, and that's how we increased the interval for the dosing. But in terms of others, I'm not sure. So Dr. Griffin and Dr. Davidoff.

DR. GRIFFIN: I think there is something to do. Just because you are at increased risk does not mean you're not going to take the drug. It means it may change your opinion about whether it's appropriate or not, and there are now recommended therapies for prophylaxis for people who are at high risk.

So if you are elderly and you are using one of these NSAIDs, then maybe you should be on a PPI or myesoprositol as well.

DR. BRASS: Which really means it's not OTC. Again, if you are asking -- If the conclusion is

that you can't do it unless you do some other things, then you're talking about really radical change in the behavior, and I don't think we are there, and I think we are just talking. So that's a --

DR. LAINE; This is labeling, but aren't we really saying, if you have these -- I mean, I assume we're going to say something like, if you have these, see your doctor. We're not going to say don't use them, if we put this in labeling, but --

DR. BRASS: So you're talking about that, again, a person under age X years old could not use this drug safely OTC without supervision?

DR. LAINE: No, just to tell them that the risk is higher, and perhaps inform them to consult their health care professional.

CHAIRMAN CANTILENA: Yes, Dr. Wood? Then Dr. Katz.

DR. WOOD: This is sort of tangential but important, I think. I think it's really important that we distinguish in our conversations about this between relatively high dose and low dose aspirin. I think we would be doing people an incredible disservice if we put the elderly off taking low dose aspirin because of fears of -- using it for cardiovascular prophylaxis, because of these fears.

It would seem to me reasonable that we

should confine our discussions to the higher doses, given that the low dose is a prescriptive indication anyway, not an over-the-counter indication. Is that fair, Lou?

CHAIRMAN CANTILENA: Yes, I think that's probably the easiest way out of this.

DR. WOOD: Yes, right.

CHAIRMAN CANTILENA: Dr. Katz?

DR. KATZ: In terms of the pain management side, an individual with chronic pain who is at high risk for developing some complication for NSAIDs should be managed by one of the pain management alternatives that does not confer that risk. That includes tramidol, opioids which in that particular population would be a substantially lower risk, physical modalities, psychological modalities, physical therapy. There are acupuncture, implantable devices of one kind or another. There's all manner of treatment approaches to pain in patients with those particular risk factors.

So proper management of those patients should be to clue them in that they should see their health care provider and consider other alternatives. You know, if there are a lot of people out there at high risk for development of complications from NSAIDs, OTC NSAIDs, who are in fact using them for

chronic pain, they shouldn't be.

CHAIRMAN CANTILENA: Yes, Dr. Davidoff?

DR. DAVIDOFF: Yes. I was going to say much of what Dr. Griffin and Dr. Katz have said. But to extend that a bit, it seems to me there are other things people can do, if they look at the box and are in some sense at increased risk because they are older. One is that they can be more alert to potential side effects.

I mean, some of those are moderately subtle and are easily overlooked, but if you are more sensitized to the possibility, you might in fact get yourself taken are of more quickly.

The other was really that there are other options that they might choose. I mean acetaminophen might work just as well.

DR. BRASS: I realize we're going to get to the labeling, and so I don't want to talk about that specifically. But I am really concerned about this drift, not so much that any of the recommendations are inappropriate, but I have grave concerns about being able to communicate them meaningfully in a nondistracting way on two square inches, and that -- So again, I raise this issue of the elderly, because these are predictable consequences when you go down there, and I don't think

they are reasonable alternatives, and that, is the magnitude of the risk we are talking about for the elderly justify these kinds of draconian measures or is simply the other risk modifications that are going to be put in place going to encompass the elderly sufficiently?

Again, that's just not clear to me.

DR. LAINE: I was just going to say, in most of the studies the relative risk increase with elderly is just as much as the others, and actually in many higher than the steroid, higher than the Coumadin one.

So I would suggest, let's -- It's not modifiable. It is at least as high as most of the others.

DR. WOOD: Yes, and being elderly is risky.

DR. CRYER: And also I would say that I wouldn't necessarily consider it draconian, given that the proposed label for ibuprofen says currently ask your doctor if you are over 65 years of age. I mean, while I certainly don't want to discourage the appropriate use of aspirin, I would think that, if someone is greater than 65 years of age and is contemplating, let's say, the chronic use of aspirin, that discussion, that decision probably should be made

with the help of a health care provider.

So I don't think that putting that comment to talk to your doctor if you are greater than 65 years of age would be inappropriate based upon that need to have that discussion.

CHAIRMAN CANTILENA: We have a question from Dr. Clapp and then Dr. Katz.

DR. CLAPP: My question to the gastroenterologists is: If you separate -- and maybe it's been answered. But if you separate age 65 as an isolated parameter and you have the other considerations, Coumadin use, you know, previous GI bleed and all the concomitant use of steroids, is the isolated age factor alone a risk factor or is it a risk factor because these people are more likely to be taking the other things?

DR. LAINE:: It's clearly a risk factor, and it's on a multivariate analyses or when you look at absolute -- I won't give you all our numbers for other studies, but you know, when you look at just 65 alone or in multivariate analyses, separate it out, it's an independent risk factor.

CHAIRMAN CANTILENA: Dr. Katz, you had a comment?

DR. KATZ: I had a question. It seems like many of us would like to put more information on

that little label than can be put on it meaningfully and still be readable. The representative from the National Consumers League had made a suggestion to put a patient information leaflet in the box to provide expanded information beyond what could be meaningfully put on the 2 x 2 label.

I don't know anything about the ability or the regulatory oompha that would be required to do something like that. So I put that out as a suggestion that had been made for comments.

CHAIRMAN CANTILENA: Yes, Dr. Ganley, do you want to comment?

DR. GANLEY: Yes, you could do that. The question is --

DR. KATZ: I personally could do that?

DR. GANLEY: The answer is what impact it actually has, and how do you make people read that?

DR. WOOD; But, ah, Charley, we've got a -- we can put a book in there, right?

DR. GANLEY: Anything you want.

CHAIRMAN CANTILENA: After you open the box, though, it's probably gone.

DR. DAY: And a lot of those inserts these days that are required are like the full monograph. For example, oh, I guess, some products, it's a very, very long thing like this, and it's narrow, and it's

at a very professional, technical level. Although ours might just be drug facts with some nice additives, people would see it all folded up, and there might be a disincentive to unfold it, let alone read it.

DR. BRASS: I would just further that by saying that not all the containers are as big as this one. I mean, if you are at the airport, you may have a very small one, and putting additional information into that may not be as practical.

CHAIRMAN CANTILENA: Right. Well, if you were a sponsor and you were going to hand around a package, which one would you pick? My question. Okay. Can we go to subpopulations. I think we've had a pretty good discussion. What I'd like to do for this is to get a yes, no, to the question 1(b): Are there subpopulations. But then if you answer yes, if you would list those for us.

Again, we're not going to talk about how we're going to handle it in the labeling or other strategies, but we will have an opportunity to that under number 2. So perhaps we can start with --

DR. CUSH: Should we not say no, accepting Dr. Cryer's list, and then whether or not you want to modify that? Makes it easier.

CHAIRMAN CANTILENA: That would be fine,

but if there are other things that you want on there, then yes. So it would be yes and, if yes, you can accept his list and/or modify it. So we can start over on this side with Dr. Kopp, and then we'll just go around the room.

DR. KOPP: I'm actually going to abstain.

CHAIRMAN CANTILENA: Dr. Rumack.

DR. RUMACK: I would say yes with this list, and the only other issue to think about is change in diet or hydration, since if you are taking especially aspirin and you switch to cranberry juice or orange juice, you can change the level of the body quite dramatically, and that's something we've certainly seen in our GRA patients. But I don't know the data for the OTC doses, although I think I've said before that it worries me a little bit, given the knowledge that patients take it for longer and higher, whether we should just stick with just the OTC doses.

CHAIRMAN CANTILENA: Excuse me. Dr. Crawford.

DR. CRAWFORD: Thank you. I say yes for the list that was articulated.

CHAIRMAN CANTILENA: Dr. Cush?

DR. CUSH: Yes, I agree with Dr. Cryer.

CHAIRMAN CANTILENA: Dr. Elashoff?

DR. ELASHOFF: Yes for Dr. Cryer's list,

except I have some objections to the over 65. I tend not to like these things that were based on some arbitrary cut point used in some analysis that then kind of took over. You could have probably picked 60 or 70 or 75, and so I guess I'm against the over 65.

CHAIRMAN CANTILENA: Doctor Watkins.

DR. WATKINS: Yes, for Dr. Cryer's list.

DR. BRASS: Yes, with the caveats about elderly.

DR. DAVIDOFF: Yes. I don't have a big problem with 65. I think everyone recognizes it's kind of a surrogate, indicating that you are getting on, and it's arbitrary. I don't remember if Dr. Cryer's list included glucocorticoids.

DR. CRYER: Yes. How you relate specifically glucocorticoids on a label, I think, is problematic, but that's --

DR. DAVIDOFF: A good editor can do that. The other question that I think was unresolved -- I don't know whether it's on the table now or not, really, and that is the alcohol warning, because it seems to me that is -- It's clearly implied as a risk factor, and maybe you want that as a separate debate, but I think that has to be resolved.

CHAIRMAN CANTILENA: Yes. I think we will -- At this point, we'll keep that separate.

DR. LAM: Yes to the Cryer list.

DR. CRYER: I agree with myself.

CHAIRMAN CANTILENA: We are very happy about that.

DR. LAINE: Yes to the list. I would just say, although 65 is arbitrary, for instance, in the study that Marie Griffin showed, you could see that at 65 it perhaps started to go up, just like colon cancer screening at 50. You know, you could start anytime, but that is when it starts perhaps going up more, but agree, 64 or 66 are probably very similar.

DR. D'AGOSTINO: Yes, and again with the arbitrariness of the age, I think it's important to not diminish the fact that, as one gets older, as I get older, our risk increases, and there is a lot of emphasis on cardiovascular risk as you get older and you can't do anything about it, but to keep driving that point home -- and if we are going to start listing other things and one of the most obvious things gets left out, I'd be very upset about that.

DR. ALFANO: It is a prudent list.

DR. CLAPP: Yes.

DR. KATZ: I accept the list, too.

DR. JOHNSON: Yes, with an acceptance of the list.

DR. UDEN: Yes.

DR. WILLIAMS: Yes, accepting the list.

DR. NEILL: Yes.

DR. PATTEN: Yes.

DR. WOOD: Yes.

DR. DAY: Yes.

DR. COHEN: Yes.

DR. GRIFFIN: I'm not voting, I don't think. I agree with the list, but --

CHAIRMAN CANTILENA: Than you for your opinion. Okay, very good.

Now we will then proceed to 2, 2(a), which is based on this discussion: Should additional warnings or other risk management strategies be considered?

Now we are broadening it. We are talking about the list. We are talking about specifically the label, and we have asked the FDA to put up the drug facts label for aspirin, just for your reference. This actually -- we can do it just, as I said, for GI, and we can do a yes/no. Should additional warnings or other strategies be considered? If yes, if you would specify what types of things you would like to have done with all the usual caveats for follow-up and studies of the effectiveness of change. But I think we are ready to get into this discussion. Does anyone have any --

DR. GANLEY: Lou, could I just let people know what this is, so that they are clear on it. This is the drug facts label that would be required to appear on the outer package. This is essentially the labeling that was proposed in the tentative final monograph or proposed rule in 1988 with the exception of the alcohol warning where it says, if you consume three or more alcoholic drinks, etcetera.

Then there is another warning you see under there where it says "Important. See your doctor before taking this product for your heart or for other new uses for aspirin." We haven't talked much about that, but there was, I believe, a 1993 proposal trying to have people not just start using it, but also to let them recognize that this may actually benefit your heart. It may not convey it in the best way, but I think, if we are going to put information on a package that tells of all the bad things, you don't want to drive people away from actually using it.

Dr. Hennekens pointed out, I think, that I think 50 percent of the people are -- 50 or 60 percent of the people that should be on it are on it, and that means 40 percent off. So you don't want to create such a label that people don't want to take it, too.

So just keep that in mind. If people want to comment on that part of it, too, we can always work

on that to actually encourage people to see their doctor to use it for the heart, but to recognize that there are problems and not to just start it on your own.

Everything else on there is proposed, and that's where we are trying to get some answers today.

CHAIRMAN CANTILENA: All right. So as I understand the question, you are asking for items in addition to what is already there.

DR. GANLEY: Well, there are things on there that cover some of the issues. I don't think the elderly is on there. Corticosteroids, I don't think, is on there. I can see the bottom where it says ask a doctor or pharmacist before use, if you are taking a prescription drug for anticoagulation (thinning of the blood). So it covers some of the things.

DR. WOOD: But wouldn't you want that on -- Even though that might appear redundant, would you not want that on also as a warning?

DR. GANLEY: That whole section there is a warning. You see where it starts. Warnings start until it goes all the way down to Directions. Okay? So all those are warnings. The way the label was crafted was to -- is to have consistency amongst labels, so that, for example, hopefully, in several

years people will know what section to look for, for a drug interaction. There will be consistency among all these labels. So they will know to go ask a doctor or pharmacist before use if you are taking.

So, you know, five years from now everyone is going to know, well, if there's drugs that I shouldn't take with this medicine, they are going to be listed in there. So it's a consistency aspect of it. All those are considered warnings under the regulation.

DR. WOOD: Charley, what would you feel about when you are dealing with this statement, "Important, see your doctor before taking this product for your heart or other new uses of aspirin" -- As you well know, there are other secondary preventive strategies that are also very effective post MI. Is there an opportunity there not to advertise that directly, but to make the point that there are other therapeutic strategies that ought to be considered that they need to be --

DR. GANLEY: Well, again, I guess there's certain limitations of how much information.

DR. WOOD: You could work on the wording is what I --

CHAIRMAN CANTILENA: Yes?

DR. DAY: Excuse me. Can I get Dr. Ganley

to comment on the following. It is a warning section. It looks like there's four things. The eye scans down. There's Reye's syndrome. There's allergy alert, alcohol warning, and Important.

There are really five things. Aspirin may cause stomach bleeding. That is a separate idea. It may happen to people who drink alcohol, but there is some sense that that is a risk as well, in and of itself. Shouldn't it be on a separate line?

So I would not be proposing to add anything to the label, but I would want it pulled out, because a consumer could go down and see alcohol warning, say, oh, I don't drink, and they don't read further. So they go down to Important and totally miss that.

DR. GANLEY; Yes. I didn't mean to imply that, but all I'm saying is, when we talk about warnings, the "do not use" is a warning under the regulation.

DR. DAY: Right, and I'm --

DR. GANLEY: You can add where you think it needs to be, if it's --

DR. DAY: Pull it out on a separate line so if there's five things, you can see five things would be my recommendation.

CHAIRMAN CANTILENA: Okay. So you've

already answered your question. There was a question here from Dr. Clapp. Dr. Uden also had a question also for Dr. Ganley.

DR. CLAPP: Is there any -- What's the rationale for the order in which the items are listed under "Ask the Doctor"? Is this according to the prevalence or -- because --

DR. GANLEY: There is no required ordering of that.

DR. CLAPP: And it's not alphabetical either. So I'm looking at this.

DR. GANLEY: They don't have to list it one after another. It can be across the line. We just did that for clarity, but what will happen in packaging -- You know, we have to be sensitive, too -- is that companies have so much space on a box, and they will move the ordering around, depending on how much space is on a line and what fits in there.

DR. CLAPP: When I look at the "Ask a doctor before," you have then asthma, ulcers, bleeding problems. It doesn't even seem --

DR. GANLEY: There is no -- A company can move those around in any position they want.

DR. CLAPP: I don't get the logic, but perhaps could there be a recommendation that the most likely side effects be the first one listed, because

you are going to drop off in reading.

DR. GANLEY: If that's what people --

DR. CLAPP: That's my recommendation.

DR. GANLEY: Okay.

CHAIRMAN CANTILENA: Okay, Dr. Uden. Actually, what we will do is you can incorporate not only things that you want to add but alterations that you would like to see in this label.

DR. UDEN: Dr. Clapp, those aren't all side effects, but to Dr. Ganley: Am I to take it that this issue of the indication for the cardiovascular use of aspirin, there is going to be no packaging which says that aspirin is indicated for whatever the terms, you know, primary and secondary prevention? I assume that's not going to happen. Is that correct?

DR. GANLEY: That is not a consumer OTC indication.

DR. UDEN: Okay. Then my second question was: So you are not going to probably see 81 milligram packaging which is directed toward that?

DR. GANLEY: Could you repeat the question?

DR. UDEN: So then we are likely not to see packaging with 81 milligram tablets in there that are specifically related to the cardiovascular issues in terms of, you know, like it was going to be

Claritin hives and Claritin allergy. So it wouldn't be Bayer aspirin heart. We're not going to basically see that type of stuff?

DR. GANLEY: I don't know. They can put pretty much -- because it's marketed under a monograph, okay?

DR. UDEN: Okay.

DR. GANLEY: And you heard somewhat yesterday of what our regulations require on the outer package. They could call it pretty much anything they want with the risks that our compliance folks would be viewing that if they called it Aspirin Heart, that that would be making it an implied indication. It's a very-- You know, I hate to be more so confusing about that, but there are certain things that are put on packages that really imply an indication. Okay? And sometimes our folks in compliance will look at that and say they are just making that as an indication when they really don't have the data.

It's usually people trying to make a claim when they don't have the data. In this situation, it would be making a potential OTC claim for heart use when they don't have that claim as an OTC drug product. They have it for professional use.

Now I think, if you want to address something about encouraging people to use it for their

heart, you go along the line of the "Important, see your doctor" phrase, but again there is a potential if someone called a drug -- you know, an OTC drug product Aspirin Heart that our compliance folks would look at that as an implied claim and potentially go after them.

DR. UDEN: Thank you.

CHAIRMAN CANTILENA: So, Dr. Ganley, just to be absolutely clear, really what you are saying is under uses you would not have the heart indication.

DR. GANLEY: You would not have it. That's correct.

CHAIRMAN CANTILENA: But, obviously --

DR. GANLEY: If you look at an 81 milligram aspirin product, if you go down to the directions it will say with the adult -- This is a 325. So it's one to two -- I think it says one to two caplets. It would say four to eight for an 81 milligram.

DR. CRYER: Dr. Ganley, would the 81 milligram packaging differ in any other way from the 325 other than what you just mentioned?

DR. GANLEY: On the principal display panel, it would have to say that it's 81 milligrams.

CHAIRMAN CANTILENA: Dr. Brass, then Dr. Rumack.

DR. BRASS: I believe the question on the table is gastrointestinal risk management. So I'd like to return to that, and that I think the areas of concern and the objectives are dictated by our previous discussion.

I think that there is an opportunity for a little bit of symmetry with what we did yesterday that might be helpful in terms of consistency in labeling. So that, for example, yesterday we talked about "do not use with other acetaminophen containing products" as being an explicit warning.

I think in this case the importance of "do not use with other _____ products" is also going to be a critical warning. It's a blank here, because I don't know what the best way to convey that is. I suspect it's other pain relievers or something like that, that carries the syntax across the entire group, but I think some validated testing, warning, like that would be important.

Similarly, yesterday again we had the problem of the risk of exceeding dose. So I think again in the case of symmetry, we have the opportunity to add something that says "do not take more than," using the corrected language from yesterday, "the indicated or recommended dose; taking more than the recommended dose may cause stomach bleeding and

potentially kidney," if you want to add that, too. But again the symmetry of the warning about multiple use and explicitly saying what the risks of exceeding the dose are, I think, might be an effective way to convey to consumers the importance of following the label indication.

We already have the language with respect to anticoagulants. I do not know how to communicate corticosteroids. I suspect steroids might be the best way, but I actually don't know what would be the best way, and I don't think there is a disease surrogate.

Some of the ibuprofen labels we've seen simply says "any other drug," and again adopting the broadly generic may be the best way, but I think devising a way to communicate that concern would be optimal.

Then I have already outlined my confusion -- Oh, for underlying disease, we already have if you have stomach problems, and for the elderly I remain unsure what's the best way. We have a proposed ibuprofen label that is draft label F in the package of labels that does say -- incorporate language "over the age of 65, contact your doctor."

While I can see the prudence of somebody over 65 seeing their doctor, I'm not sure that is actually going to modify consumer behavior in the real

world with the enormous prevalence of these medications and availability of these medications, and whether or not -- how to communicate that risk effectively, I don't know how to do that.

CHAIRMAN CANTILENA: Okay, other comments? We have Dr. Rumack and Dr. Davidoff.

DR. RUMACK: I think I'll -- Unless we are going to come back to it, since we switched gears again, I'll wait until we go to number 3 to discuss my question.

CHAIRMAN CANTILENA: Thank you. Dr. Davidoff, is this on this topic?

DR. DAVIDOFF: Yes. To extend the suggestion that has been made about pulling out the "aspirin may cause stomach bleeding" warning, I would not only agree. I would urge or suggest that there be a subhead bolded and like sort of analogous to the Reye's syndrome and alcohol warning statement saying "Bleeding alert: Aspirin may cause stomach bleeding."

Even though I realize that the issue on the table is stomach bleeding, I think it's going to be hard to separate stomach bleeding from other important kinds of bleeding related to aspirin and other NSAID ingestion, namely, the bleeding that is associated with a whole variety of things, like if I'm a dentist, I want my patients to stop taking aspirin

or I want to know if they've been taking aspirin before they get their tooth extracted, or if I am a gastroenterologist about to biopsy somebody's polyp, etcetera, etcetera, etcetera.

Subtle, genetic abnormalities of platelet function are not at all uncommon, and those patients are at significantly increased risk. So I would suggest that we at least consider, if not now, later, that the statement be "Aspirin may cause stomach or other bleeding." I think that is a fair and accurate statement, and that belongs somewhere.

As to the issue of steroids, I would think that a useful way to convey that would be to say "Drugs related to cortisone." My concern about using the term steroids, which I agree is in some ways not unreasonable, but I think that's gotten so confused in people's minds with anabolic steroids for conditioning and building and bulking your muscles that that might be more confusing.

The drugs related to cortisone -- most people even who are taking prednisone sort of talk about taking cortisone. So that may be a useful approach.

Finally, on the question of organ specific kinds of information, I wonder whether it might not be appropriate to consider, if we are going to be talking

about redness or swelling and pain is present in the painful area, if we are concerned about early warnings of GI bleeding and getting people being taken care of sooner rather than later and preventing them from getting much worse or dying, to include some wording about "stop use and ask a doctor if any new symptoms appear, particularly faintness, black stools or vomiting blood" or something along those lines.

CHAIRMAN CANTILENA: Okay. I think what we will do -- There's a lot of comments, and I think we are starting to actually answer the questions completely. I guess what I'd like to do is, unless someone wants a clarification, Dr. Johnson, after your comment, why don't we go around and get a sense for whether or not changes are what you want, and specifically, we can either add to or subtract or modify. But I think we have to sort of come to closure on this, because we have other things to cover. So go ahead, Julie.

DR. JOHNSON: Okay. I think I might need some clarification from FDA, and my confusion is really sort of the consistency and wording between the aspirin -- really between all four of the products relative to "stop use and ask a doctor if" and related to sort of worsening stomach kind of symptoms.

For aspirin, the only thing that is listed

is "any new symptoms appear," which to me is not very useful. For ibuprofen -- and I sort of get confused which ibuprofen label to look at, but the one I'm looking at right now says "stomach pain or upset gets worse or less," which if you read that literally says if it's new stomach pain you don't call the doctor, because that's not what it says. It's only if it gets worse or less.

I guess I like the wording that is on the naproxen label which says "stomach pain occurs or lasts, even if symptoms are mild." So I'm wondering if you can clarify, really, I think a very, very broad range of messages and what the basis for that is.

CHAIRMAN CANTILENA: Dr. Ganley, do you have a -- As long as you give it back, I'll let you have it.

DR. LUMPKINS: I think basically what you are seeing is a function of when the products were approved. What you are seeing is labeling that was developed through the OTC monograph process, and then you are seeing a number of products that were approved by different people at different times, and they had different ways of addressing the problem of stomach pain.

DR. JOHNSON: So as new products are added or sort of better understanding -- I guess my

impression was in a drug class. So, for example, NSAIDs, that there was consistency across the labeling. That's not the case?

DR. LUMPKINS: Not actually.

CHAIRMAN CANTILENA: Only in the monograph.

DR. LUMPKINS: Yes.

DR. JENKINS: Maybe I could help you understand that. I think the labeling you are seeing up here for aspirin is the proposal we put out in '88. Is that correct? So what you are seeing up there was written in 1988 in the proposed rule for the monograph products.

Subsequently, you have the approval for the OTC versions of these products that, hopefully, over time have gotten better wording as we have learned more and as we have negotiated with sponsors of those new drug applications, because, remember, the three NSAIDs that are available over the counter are under new drug applications, and that is more of a negotiation process with each individual sponsor.

I'm glad to hear that you think that the later versions of that wording are better than the earlier versions. So the wording that might come in the final rule could be closer to what you are finding that you like in the more recent versions, if that's

what you recommend.

CHAIRMAN CANTILENA: Right, and I think also one of your recommendations could be that we standardize it, you know, so that it was simple for the consumer.

Okay, let's start over on this side. What I'd like you to do is just say yes or no in terms of should we modify the label, add warnings or other programs to reduce risk for nonsteroidals or aspirin, and then if you would list under GI some of the things that you feel are the most important toward that end. We can start over here. Dr. Griffin.

DR. GRIFFIN: I would say yes, and I would think that it could be fairly comparable to what we just talked about as far as subgroups at higher risk.

I guess I'm a little concerned about this sort of warning people away from using aspirin for cardiovascular indications, and then not having the information. I guess I would maybe like the committee to consider a better way to inform the public about talking to their doctor about taking the aspirin for cardiovascular indications, and that the lower dose is associated with a lower risk.

It seems to me that consumers should know that. I don't know how that could be incorporated into this label.

CHAIRMAN CANTILENA: I don't think anyone of us knows exactly. We'll certainly include that in our recommendations to FDA. Dr. Cohen?

DR. COHEN: I also think we should go back to Dr. Cryer's prior list. I think there is a word that we could use possible that some people would understand when it comes to the combination therapy.

NSAID is, I think, a term that is -- It's coming into more common use, at least for some people. I see it in drug information leaflets, for example, that are intended for consumers, and at least there's a chunk of people out there that might understand what it is so that you could say, you know, that this is an NSAID and it shouldn't be taken in combination with other NSAIDs or other pain relievers, etcetera.

CHAIRMAN CANTILENA: Dr. Day?

DR. DAY: I agree with putting the various things on we have discussed, but I want to reemphasize that it has to be communicated well. So in the warning section each chunk should stand out by itself, have a little subtitle before it, and I'm not sure that I like the final one about "Important, see your doctor" and so on, but why is that important and the other ones aren't? Each one should have a subtitle which is about its content.

There's Reye's syndrome. There's allergy

alert. There's alcohol warning. There's bleeding alert or whatever you want to call it, something softer, and then it could be "New Uses." So name what a thing is, and then put everything that goes with it there, and don't subsume things within the same category that don't belong there.

Therefore, we would be obeying two very strong principles that have been demonstrated in cognitive science over and over. When you have a lot of information, chunk it. Put together what goes together, and code it. Name it what it is named. And if you don't do that, if you sprinkle it all around, don't name it or put things together, people aren't going to get it.

CHAIRMAN CANTILENA: So your vote is to simplify then, which is what they are asking for?

DR. DAY: I would say not just to simplify, but to make very clear how many different warnings there are, and only put together what goes together for a given warning, and label each. Okay.

CHAIRMAN CANTILENA: Dr. Wood?

DR. WOOD: I would go with the list we have already covered, and the only additional things I would say are that, you know, if you think about the Intel logo -- you know, "there's Intel inside" logo -- I would encourage the agency to try and come up with a

similar way of identifying things like "acetaminophen inside," and "nonsteroidal inside" with some sort of logo.

I'm not being facetious, actually. I mean, think how successful the Intel logo has been. You know, it even plays a sound, and that we come up with that; because I think people are not going to pick up easily on these things.

The other thing that I want to raise is this alcohol warning. I'm not persuaded that the alcohol warning has much in the way of scientific rationale, and it gets pretty big play here.

DR. CRYER: I think the gastroenterologists in this corner of the table, Doctor, would agree with that last statement about alcohol.

DR. WOOD: You mean that you think it does have --

DR. LAINE: No. We feel extremely strongly. I mean, we can talk about it now or later, but we feel strongly about taking -- that we would take it out.

DR. WOOD: So I don't see any data to support it, and I think, in the absence of data, that it should come out.

CHAIRMAN CANTILENA: Okay. Let's --

DR. CRYER: In fair balance, I must say that there are data that are out there. The data are mixed, and there's no consistency of data.

DR. WOOD: Given the limit that we can --

DR. LAINE: I must say, I think the majority, though, of epidemiologic and randomized controlled trials fail to show an association of alcohol, and since we have repeatedly been talking about this idea that we want data before we make broad recommendations, it makes no sense to me that this would be there.

CHAIRMAN CANTILENA: Okay. So, Dr. Wood, your comments, including the strong consideration that that be removed. Dr. Patten.

DR. PATTEN: Yes. I agree that additional warnings or other risk management should go into place. Some specific suggestions under the "stop use and ask a doctor if" for aspirin. I really don't see anything here that would pertain specifically to GI bleeds, and since that is a hazard, I think some of the -- No, I see that there, "ask doctor before use if you have," but I don't see anything under "stop use and ask a doctor if." I think something should also be mentioned in that category.

I think we could start the learning process with regard to this category of NSAIDs, but I

don't think that -- I don't think we should put all our confidence there. It could be done something like this perhaps. Let's take aspirin, for example.

"Aspirin: Aspirin is an NSAID. NSAIDs are pain relievers. Do not take aspirin with any other NSAID pain reliever," or something like that to give people time to begin to use this new term in this new category. But I think they would have to have the information both ways.

With regard to the matter of using the product for your heart, and you need to see your physician and so on, the information is out there. People are using aspirin for their heart without seeing their physician. So it seems to me the risk is great that they are using it at too high a dose, and I don't know what you would suggest to be done about that, but I think it is happening. So I think we shouldn't sidestep that problem.

DR. WOOD: Well, there are two potential doses. I mean, there is the dose that you might want to carry around in your inside pocket for the day you have your chest pain, and that you want to take acutely, and there is the dose you would want to take chronically. That's going to be tough to deal with if you get into that in too great a detail.

CHAIRMAN CANTILENA: All right. Dr.

Neill?

DR. NEILL: We're talking still about question 2(a). Correct? I just wanted to make sure, because there's a lot of other extra comments. Related to the GI bleeding specifically, and given the section 4 see analgesic labeling that we got yesterday, I like Appendix F for ibuprofen with the caveats about removing the alcohol warning. I would not, in removing that, want to get rid of the "ibuprofen make cause stomach bleeding." That does need to be separated out.

For aspirin I like the proposed labeling in Appendix B with the caveat that I do think staff need to work with industry to find some way to resolve the inherent conflict about "see your doctor before taking this product for your heart or for other new uses."

That language is awkward. We have already discussed that sort of inherent problems of knowing that people will take this. To clarify in my own mind, the risk when taking the low dose, 81 milligrams a day, accrues from how long you take it, not from the fact that it's a low dose. So people taking that low dose over some long period of time have a higher risk of GI bleed than somebody who may take a maximum dose of four grams of aspirin a day for three days. Am I

thinking wrongly about that?

So it's not that the risk is lower with a low dose. It's that, you know, people are taking this every day all the time at a low dose, and their risk is higher, and they don't know it.

CHAIRMAN CANTILENA: Dr. Williams?

DR. WILLIAMS: My vote is for yes for the previously described list.

CHAIRMAN CANTILENA: Dr. Uden.

DR. UDEN: Yes for the previously described list, and I think Dr. Johnson will say this, but I will say it first. I like the part in naproxen where it says that, "if stomach pain occurs or lasts, even if symptoms are mild" should be added.

I also agree with Dr. Davidoff that there should be something in there about vomiting blood or black stools.

CHAIRMAN CANTILENA: Thank you. Dr. Johnson?

DR. JOHNSON: Dr. Uden stole my thunder.

In terms of the cardiovascular benefit, and I know we are not exactly talking about that, but is it possible to -- Dr. Ganley, is it possible to be explicit and say something like "aspirin may help your heart; talk to your doctor," or is that too --

DR. GANLEY: No, I think you can make a

recommendation, and we will look at it. I don't know if you want to make another comment, John.

DR. JENKINS: Yes, I thought maybe I could help clarify some of the things about this cardiovascular indication, because the labeling we passed around a little while ago, looks like this, the professional labeling for aspirin, has all those cardiovascular indications in it.

That, in effect, would be the prescription labeling for aspirin, but there are no prescription aspirin products. Therefore, it's called professional labeling which gives doctors the information they would have for prescription aspirin if they were using it for this indication.

It's not unlike ibuprofen which has OTC uses for analgesia and fever for short term use, but we still have prescription ibuprofen for arthritis chronic use. It's not inconceivable that a company or a sponsor or someone could petition the agency or submit to the agency a proposal that the cardiovascular indication should be over-the-counter indications. That would be clearly something we would have to have data, and we would probably have at least one meeting of this committee to further discuss such a proposal, but that's the problem we are running into now, as Dr. Ganley described.

You can't put an indication on the OTC box that's not an OTC indication, but we know that people are commonly using the OTC product for that professional or "prescription" (quote/unquote) indication, and we are not currently able to give them the advice and maybe the warnings that we would like to give them. That comes up in question number 3. So you may want to save some of that until question number 3.

I was going to try to clarify that distinction. We essentially have prescription aspirin indications and nonprescription aspirin indications, but we only have nonprescription products.

DR. JOHNSON: Okay. So I'll save that.

In terms of the other things, I agree with most of what everybody else has said, and I think that the later iterations of labels got progressively better, and I think that probably consistency is a good thing. I think probably in some ways the worst of the labels is the aspirin label. I guess may be that's because it's the oldest.

So I would argue for consistency in language where that is appropriate, which I think is in most of the cases. I think that we want to avoid language that really conveys nothing meaningful. So, for example, under ibuprofen -- and I think this is

the old -- I don't know, the first ibuprofen label in our packet -- it says "ask a doctor or pharmacist before use if you are under a doctor's care for any serious condition."

I'm not sure that conveys anything meaningful to a patient, because I think some patients may have what we might think of as a serious condition, and they don't view it that way. So, again, I think I guess I don't believe that general information like that is probably very useful.

CHAIRMAN CANTILENA: Okay, thank you. Dr. Katz?

DR. KATZ: I have a couple of comments, some of which are actually related to the question on the table.

The first comment that I have is that I'm sitting here with this very nice, huge bottle of aspirin, and I can't make out the back of the label, and I'm 41. So, you know, maybe I should look into getting glasses, but I have 20/20 vision, and I can't read it. So I think, you know, we are having a long discussion about all these wonderful things that ought to be put on the back of the bottles, and this is probably as big as these bottles get, and I don't think that we are being realistic.

I think we need to think about that, and

maybe, as Dr. Johnson was saying, we can take a look at the very end and see what can be deleted, either in this meeting or offline afterwards. But I think that we are really being very unrealistic about what people will read when all is said and done.

Having said that, I have a few specific comments. One is that I agree with -- I like Dr. Woods' idea about having some sort of a figure, some sort of callout in front that says this is this type of medication, because I think at the end of the day some sort of pictogram may be the most effective way of communicating to people what class of medication this is.

I don't think it's so terrible that, when the first time somebody looks at this on a counter, they won't understand what it means, because I think, just as I didn't understand what the "Intel inside" logo meant when I first saw it and figured it out only after I saw the logo and got intrigued by it, I think this could actually be part of the teaching process.

In terms of the specifics of the GI things, I think that the warning, as it stands on the drug facts label right now, which is "ask a doctor or pharmacist before use if you are," is not strong enough. I think that, to me, I can't think of a reason why somebody should be on Coumadin and a mixed

NSAID or aspirin for pain, and I can't think of a reason why somebody should be on corticosteroids and mixed NSAIDs these days as a first line of treatment, given that there are other options that are much less risky.

So I would favor a language more like "do not take this if" blah-blah-blah, "unless you are under a doctor's care." I think that we have -- GI bleeds and deaths from GI bleeds in this country are a big problem. They are a much bigger problem than the acetaminophen overdoses we heard about and spent a lot of time talking about yesterday, and I think we have to take a stronger stand, since it is obviously still a problem despite the sorts of labeling that we will be seeing.

If a bleeding callout, as Dr. Davidoff suggested, would be a more effective way of getting that point across, I would be in favor of that, but I think this sort of language is way too weak to accomplish what we need to accomplish here.

As far as the alcohol thing goes, I'm sorry. Not being a gastroenterologist and being as familiar with the data, I sort of have to fall back on good old fashioned common sense. It seems to me that alcohol causes stomach ulcers and varices and platelet problems. Nonsteroidal anti-inflammatory drugs cause

stomach ulcers, bleeding problems. To me, two and two makes at least four and, if it doesn't make five, that doesn't really bother me too much. So I think it would be a big step backward to try to remove the alcohol warning.

CHAIRMAN CANTILENA: Thank you. Dr. Clapp?

DR. CLAPP: Well, first with the alcohol warning, my impression is that the less you can have on these labels, the better. There is no basis in data or reality that really supports an alcohol warning. I would say remove it.

My sidebar to the gastroenterologists just now was doesn't alcohol abuse cause derangement of your PT and PTT on the basis of liver destruction and, therefore, wouldn't you have more likelihood to bleed if you take NSAIDs, but he says it's a very tiny risk. I don't know. I'm not a gastroenterologist or a hepatologist. So I have to depend on you folks who are to give me some direction. But if, in fact, there is not a risk that is statistically significant, I would remove the alcohol warning.

Secondly, as far as the other indications, I think they should be placed as Dr. Cryer listed. The simpler, the better. I would have to endorse wholeheartedly Dr. Day's suggestions about chunking

and putting things in a way that are more likely to be read.

I think the FDA might consider a standard approach to warnings such that the most likely or the most devastating be put first, because we all know our reading falls off as we proceed, and asthma does not grab me as a high risk indication for deadly outcome with aspirin use. We all know the syndrome, but how many of us have ever run into it. It's not as common as a GI bleed.

Other concerns I have include, just as -- I'm sorry, I don't know the neurologist's name but appreciated his -- You know, I am a little older than you. I couldn't read that label without stretching my arm, and I'm sure that 65-year-old people who need to read the label will have a very difficult time doing that. So my next suggestion is that the FDA look into how they can extract or make the manufacturers extract the most pertinent information from the back of the box and put it on the bottle so you get the high points in big print and keep moving with that.

Those are my suggestions.

CHAIRMAN CANTILENA: Thank you. Comments from Dr. Alfano?

DR. ALFANO: Yes, thank you. A couple of comments on this issue in general and then a few other

comments.

The first comment, and again in "first, do no harm" arena: I was pleased to see both Dr. Katz and Dr. Day in the course of our discussions here point out the need for continuing label comprehension studies. Even label suggestions that we might make as a panel need to be studied for unforeseen misinterpretations on the part of the consumer.

Like others here, if the data is not strong for an alcohol warning with this class, we ought to remove it, because we haven't given consumers a place to go. If the earlier approach was to level the playing field, that's fine. It puts things into neat little boxes from an agency perspective, but it doesn't necessarily help the consumer who is trying to find a medication he can take if, in fact, he or she has consumed alcohol.

A third comment is I have some heart for Dr. Brass's suggestion early on, that we might want to differentiate over-label usage from labeled usage in this category, like we did yesterday, because it ratchets up the warning that it's serious if you exceed these label recommendations, and so this might be an opportunity to do that.

Then I guess the final comment revolves around an earlier remark I made. You know, we have a

tendency to want to have these things with very similar labeling, and earlier today Dr. Laine made the comment, which I tend to agree with, that it doesn't make much difference if it's relative risk of one-sixth or two-four. But we do have some nonsteroidals that, at least according to the Langman data, are substantially higher than that.

With naproxen, it's six or nine. It depends on how you look at it, and ketoprofen at 34. When you start to get that different, you know, fitting them all onto the same label doesn't make as much sense to me. Thank you.

CHAIRMAN CANTILENA: Thank you. Dr. D'Agostino.

DR. D'AGOSTINO: Yes for the GI bleeds, and I'm going to yield my three to five minutes of elaboration to my GI colleagues.

CHAIRMAN CANTILENA: Thank you. Your time is yielded. Dr. Laine.

DR. LAINE: Yes with agreeing with most everything that he said. I actually agree with the idea that we should have actually uniform language across the different NSAIDs and, frankly, across aspirin, so it doesn't get confusing as it was stated.

I clearly think we need to break out the stomach bleeding into a separate warning, and I would

use the stomach or intestinal unless you think that intestinal is too confusing for people understanding, and just leave it stomach or stomach or other, as you mentioned.

I agree with the -- I think it's important, the five risk factor rule we talked about. The fact that increasing dose increases risk is reasonable.

Let me actually spend most of my time talking about the alcohol, just again to try to defend removing it. A couple of points just to mention. One, alcohol and alcoholism doesn't cause ulcers. So we need to keep that clear. *H. Pylori* does, and NSAIDs do, but alcohol has not been documented to cause ulcers.

Second, the issue of alcohol versus cirrhosis. There is no doubt that the prothrombin time is markedly abnormal in alcohols who have advanced cirrhosis. Only 15 percent of people who are alcoholics may develop cirrhosis, and only a certain proportion of them will develop a coagulopathy and then, you know, if they happen to have an ulcer, yes, it's possible they might have an increased risk of bleed, although I don't know of that data. But once you get to the cirrhotic stage, there's a far more important reason that nobody should be using NSAID

except -- unless it's very carefully considered, and that's because of the renal side effects that we'll talk about.

So I think you've already got that cirrhosis taken care of on the renal side effects.

Finally, the issue of additive versus synergistic that people talk about, that two plus two equals four. It is important that it be synergistic, not additive.

Let's say we accept that two percent alcohol risk and two percent for aspirin risk to make up numbers. If I'm drinking alcohol and I'm taking -- If I take aspirin or I eat a chocolate chip cookie, I have the same two percent increase absolute risk of developing GI bleeding. So the point is it doesn't matter what I do, I still have the same increase in alcohol and the chance of developing an alcoholic -- a bleed associated with alcohol.

I guess my point is the two percent additive is additive to anything, and unless you want to tell the FDA to put it on all alcohol that that causes bleeding, I think that's really not the issue here. The issue is does it increase the risk significantly if you use NSAIDs as compared to if you don't use NSAIDs, and the point is, no, it doesn't. The relative risk would be the same, whether you used

NSAIDs or didn't use NSAIDs.

CHAIRMAN CANTILENA: Dr. Cryer?

DR. CRYER: I agree with most everything that's been previously mentioned. I just would like to emphasize two that have not received as much emphasis, and that was the previously made comment that "do not use with" and the blank would be some words to describe these other pain medicines or anti-inflammatory drugs.

Then I think it really is important -- I kind of sat here and mulled over for a few moments this issue of stopping if there are symptoms of GI bleeding, specifically vomiting blood or black stools, and I really think that's important; because I don't know how many patients I've seen who have presented to the hospital with melena on an NSAID who had no idea what that melena, what that dark stool represented.

CHAIRMAN CANTILENA: Good. Thank you. Dr. Lam.

DR. LAM: Yes. I will respect the opinion of my GI colleague, and if there is no good data, take out the alcohol warning, and use the space to actually highlight the warning regarding the GI bleeding. As it stands right now, it is the last sentence under the alcohol warning and, if I read it, if you consume three or more alcoholic drinks, and I don't, then I

would just move on to the next box.

CHAIRMAN CANTILENA: Dr. Davidoff.

DR. DAVIDOFF: Yes. I continue to think that the suggestions I made earlier are still valid, but I have a few other things to suggest.

First of all, even though I don't know how the regulatory process would accept this, I wonder if it wouldn't make sense, considering that bottles tend to be a lot -- inner packages tend to be a lot smaller than the box or to have less space for information, to consider the same sort of things that editors have considered for a long time, and that is that in publishing their articles they have an abstract which gives you a precis of the key information. Then if you were interested in getting into depth, you read the full article.

I wonder if we might not consider the bottle as the abstract and some other instrument like the package or a package insert, or both, depending on what you can do, as the place you look for more information, and the abstract or the bottle could say "for more information, refer to the package" or the insert. That's just a thought.

I don't know how that would fit with the -- I mean whether you could tease apart the drug facts format to pick out the key things, and only those go

on the bottle, and then the rest goes elsewhere, or not. But the concept strikes me as one way sort of through this thicket of trying to squeeze out more information and yet make it readable, and that might be an alternative solution.

A couple of other thoughts. One is that this item under the warnings of "important, see your doctor before taking this product for your heart" strikes me, in connection with what Dr. Day was talking about, as sort of coming out of the blue. I mean, here you've read the uses, and nowhere does it mention heart uses or anything else, and all of a sudden it is telling you about what to do about heart uses.

I wonder if it doesn't make sense to actually move the information about uses for heart or other new uses up into the uses section and say something like, after the uses that are listed there, then say "this product can also be used for your heart and other purposes" or whatever.

CHAIRMAN CANTILENA: Yes. On that point I think, you know, Dr. Jensen -- excuse me, Dr. Jenkins was saying that that is not an OTC indication. So you actually can't have that as an indication.

DR. DAVIDOFF: But this isn't saying that you should use it that way. It's just notifying

people that there are other uses. I mean, it's alerting them to -- You could say usage alert or something, not -- I mean, because it just strikes me as, if I'm reading this and I've read the uses and then it doesn't say anything about those, and then I come down to warnings, it's backwards. It just strikes me as anomalous, and there might be a way to deal with it that way. But anyhow, for what that is worth --

A couple of very more minor things. Well, not so minor, I strongly support the notion of information about other nonsteroidals and telling which are in the naproxen label, and I think that makes more than good sense.

Finally, there's the -- One of the things that people are worrying about, "ask your doctor before you have use if you have ulcers." Well, sometimes people think of ulcers as the ulcers you get on your leg, which a lot of elderly people do. I think it should say stomach ulcers.

CHAIRMAN CANTILENA: Thank you. Dr. Brass, any further comments?

DR. BRASS: Dr. Laine had me really worried. I thought he was going to try to restrict access to chocolate chip cookies there for a minute. I was really worried.

I have -- Before we dismiss the alcohol thing, I have another question for the gastroenterologists. As was alluded to, in the ethanol abusing population GI bleeds are very common, regardless of other things, and it might be gastritis, as most common cause.

My question is: Is the outcome in an ethanol abuser who has a GI bleed different if they are on a nonsteroidal anti-inflammatory drug or not? In other words, not view it from an NSAID-centric perspective but view it from an ethanol-centric perspective and on an outcome basis.

Again, intuitively I might think they would do less well, but I don't know if there are any data to address that concern.

DR. CRYER: I would say it really would depend on the manifestations of the alcohol in that person. So if we are specifically talking about someone who has already cirrhosis induced from ethanol or from another cause and now has a variceal bleed, for example, related to that, then certainly the presence of a platelet inhibitor on board with that variceal bleed will make that variceal bleed worse.

DR. BRASS: What about presenting with gastritis, which I think is probably statistically most common?

DR. CRYER: We would call this something very different. We wouldn't say --

DR. BRASS: I apologize for --

DR. CRYER: In fact, did I answer your question? We don't even believe in that notion.

CHAIRMAN CANTILENA: Of gastritis or --

DR. BRASS: I mean a lot of alcoholics present with vomiting blood, and you do an endoscope. They don't have variceals. They don't have ulcers. They just have diffuse irritation in their stomach.

DR. CRYER: Right. And I would say that that diffuse irritation would -- Well, the blood in many cases would be related to either what we call a Mallory Weiss tear or esophagitis or ulcer disease, but specifically to say that alcohol is the cause of this endoscopic gastritis that I showed you earlier -- I don't believe that it really exists.

DR. BRASS: Okay. Regardless -- Then I apologize for my lack of specificity. Regardless of the label attached or the underlying etiology, again intuitively it would seem they would do worse if they presented with that condition and also had a nonsteroidal on board.

DR. CRYER: Well, that presumes that the condition exists. I mean, do you follow me? I don't -- What you are describing, of the individuals who are

alcohol users, is actually not a common phenomenon that we would see specifically attributable to ethanol.

I think your assumption that this exists comes from animal data in which animals were given high doses of ethanol and manifest with hemorrhagic gastritis, but ethanol, when used in the conventionally used doses, does not give this appearance of hemorrhagic gastropathy that you are describing.

DR. BRASS: Well, maybe -- Again, all I know is I admit five alcoholics a week with upper GI bleed, on endoscopy don't have varices and have some other basis, alcoholic related risk factor who, it seemed to me, would do worse if they were also on an NSAID.

DR. GANLEY; Can I just ask something, Eric? Over here. If they have no abnormalities of coagulation, I think what Dr. Cryer is saying, it's a condition that anyone else could have, peptic ulcer disease, Mallory Weiss tear, and having an NSAID on board would have no difference whether they were alcoholic and had a Mallory Weiss or alcoholic and peptic ulcer disease.. Am I correct, Dr. Cryer?

DR. CRYER: Yes, and I think Dr. Laine made that point earlier, that exact point.

DR. BRASS: Well, it's not clear to me in terms of outcome. Again, you would not want an antiplatelet agent on board anybody who is bleeding for any reason, it would seem to me.

DR. CRYER: And you list that, if you have a history of ulcer disease or other -- or bleeding problems. Okay? I think that's what he's trying to say.

DR. BRASS: Well, maybe we have a very strange epidemiology in my hospital, but we have lots of alcoholics who bleed.

DR. NEILL: I think that's why there is not a warning that says check with your doctor before using sharp kitchen knives.

DR. BRASS: But isn't alcohol a sharp kitchen knife? I mean, that's my point.

DR. NEILL: Which is why it's okay to come off, not why we should put kitchen knives on the label.

CHAIRMAN CANTILENA: No, I think Eric's point is that we see a lot of this, and I see this as well. We may not know what it's called or we may be calling it by something else, but we see this. The question is, if you have an upper GI bleed, should -- I mean it's probably not a good idea. I can't see that it would be, by any stretch, a good idea to be on

an antiplatelet drug.

DR. CRYER: We absolutely agree with you. If you have a history of gastrointestinal bleeding, I think that currently is in the label as proposed, you should not or you should talk to your doctor or be concerned about being on these agents. But our concern is without the antecedent history of a gastrointestinal bleed in someone who drinks alcohol within the range that we are discussing, we don't see that as a specific risk of concern.

CHAIRMAN CANTILENA: Okay. I understand what you are saying now. Yes, Dr. Davidoff?

DR. DAVIDOFF: I wonder if we are focusing on the wrong question We are focusing -- This discussion is focused almost exclusively on incidence, and it sounds like there's pretty much agreement that the incidence is additive, and in that sense putting the information about alcohol isn't necessarily useful. But I wonder if the real concern is not that, once you start to bleed from your alcoholism, your outcome is worse because you are going to bleed worse, because your platelet function is interfered with.

I don't know how you tease that apart, you know, the increased bad outcome risk because of being on aspirin, once you develop the bleeding. If the risk is increased just from the alcohol, then the

added risk is not for incidence, it's for outcome, worsening the outcome.

From that point of view, I would support what Eric says.

DR. LAINE: I'm sorry. Do you mean from an alcoholic gastropathy, because the alcoholic gastropathy we should keep in mind, and you have to remember, there are four layers of the GI tract, but alcoholic gastropathy, by definition, only involves the mucosa, and there are no blood vessels of any significant size in the mucosa.

You really do not get major bleeding from alcoholic gastropathy, and alcohol hasn't been associated with ulcers, which by definition the break goes into the submucosa or deeper where there are, you know, big blood vessels.

So for that reason, if you look at more modern stuff, there's very little, if any, major bleeding associated with "erosions." It's really only with ulcerations.

DR. DAVIDOFF: Well, that said, I can't argue with that since you know it better than I. But if you are an alcoholic, it seems to me -- and you looked at the overall risk of bleeding from everything, including Mallory Weiss tears, varices, ulcers, whatever, it seems to me your risks are

greater than if you are not a drinker.

If that's true, and you are taking aspirin, your outcomes are likely to be worse because you have both an increased incidence of overall bleeding and difficulty stopping the bleeding.

CHAIRMAN CANTILENA: Okay, I'm going to have to stop the discussion of alcoholism and GI bleeding and antiplatelet drugs. Eric, did you have any other -- anything other than the alcohol that you would like to add?

DR. BRASS: I think I'll quite while I'm behind.

CHAIRMAN CANTILENA: You actually lost a lot of ground in that round. Okay. Dr. Watkins.

DR. WATKINS: Just two things. One, I'm increasingly intrigued with the idea of the "Intel Inside" equivalent, especially perhaps if COX-2 inhibitors come out next and they are multiple analgesics in different classes. That might seem to me make very good sense. People would learn it over time.

The other thing is, in taking out the alcohol warning, I certainly have complete confidence in Doctors Laine and Cryer. This is their area to know that. But I'm a little surprised to hear it, and it would have repercussions, obviously, to

acetaminophen's labeling where it says this or other pain relievers. I guess the "other pain relievers" would come off, and then in effect you would be saying, if you are an alcoholic, you should be taking NSAIDs and not say a reduced dose of acetaminophen.

So the only thing I -- We never saw any data that supports that there is no difference. Someone should look at the data in people who consume alcohol and alcoholics with and without NSAIDs and bleeding and outcome, once bleeding occurs, just to make sure, because it seems to me there would be some substantial repercussions of it. But that's it.

CHAIRMAN CANTILENA: Thank you. Dr. Elashoff.

DR. ELASHOFF: Yes. I agree in general. There's two additional comments I wanted to make. First of all, the formatting of the drug facts where the word warnings is not really any bigger or spaced any differently than the things below it does not make clear that every single thing you see down until you see the word directions is part of the warnings. It should be a bigger word. It should be spaced out. That sort of formatting needs to be paid attention to.

The second thing has to do with the issue of whether we put something on as a warning depending on whether it's additive versus multiplicative. I'm

not entirely sure that we have heard that everything else that we are thinking of putting on as a warning is, in fact, multiplicative versus additive or what the kind of power considerations would be in making those sorts of decisions.

So that I have some problem with taking alcohol warning off on the basis of saying it's additive and not multiplicative when we haven't really looked seriously at all these other things to make that same kind of determination, and I'm not entirely sure how we would do it.

DR. BRASS: Just in one second, I apologize. All the others that we talked about were independent predictors and multiplicative in multiple epidemiologic and were perspective studies, while alcohol was not. So that's the only point I would make to that.

CHAIRMAN CANTILENA: Thank you. Dr. Cush.

DR. CUSH: I agree with the statements thus far. I would remove alcohol and have its space subsumed by a space dedicated to that this may cause bleeding stomach and risk factors for that.

I would also add under the "stop use and ask your doctor if you have symptoms of a GI bleed," as Dr. Cryer pointed out, and that those symptoms should also include fainting or dizziness.

CHAIRMAN CANTILENA: Dr. Crawford.

DR. CRAWFORD: I reiterate the need for additional labeling on the GI bleeding, especially the need for the labeling to help users to recognize the major symptoms of GI bleeding.

I ask for a clarification from the FDA on the rulemaking process. This morning during Dr. Gilbertson's presentation on page 10, he discussed the ibuprofen proposed rule for 2002. My question is: If the recommendations of the panel are accepted by the agency regarding the GI bleeding, would they be incorporated as comments on the ibuprofen proposed rule? I just don't quite understand how to put the two together.

CHAIRMAN CANTILENA: Dr. Ganley, can you comment on that?

DR. GANLEY: They would be comments in answering it, yes.

CHAIRMAN CANTILENA: Dr. Rumack.

DR. RUMACK: I think the idea of separating out the GI bleeding is acceptable and a good idea. I like the suggestion from across the way that we say something like this is an NSAID and don't take it with other NSAIDs, or have some sort of a labeling. That seemed like a very good idea.

In terms of the alcohol, I have a couple

of thoughts. First of all, we listened to Dr. Lee and Dr. Riley yesterday from the ALF. Despite their concerns about acetaminophen hepatotoxicity, they both indicated that acetaminophen would be their first choice in both liver disease and in alcoholics.

I don't think, if you look back at the 1993 hearings, both in June and September, the data that was presented was 16 to 18 drinks, if you look at the data on both of those hearings, and the decision was made to go with three drinks in both of these areas as a surrogate for saying alcoholics, and it does not seem to me that the hepatologists and the toxicologists would be very enthusiastic about seeing alcoholics be pushed to take NSAIDs.

I mean, that follows up from what we heard yesterday from Dr. Lee and Dr. Riley. So that would very much concern me, unless we go back and look at all of that data, as it does this whole group of drugs from these last two days.

DR. LAINE: I thought they were talking only about liver disease. They didn't say alcoholics, I believe. Dr. Watts, correct me -- because of the side effects of NSAIDs in cirrhotics. I thought they were talking about the treatment of Interferon in people with chronic hepatitis.

DR. RUMACK: That was one thing that they

talked about, but they talked about their first choice in alcoholics and in other liver diseases. If you go and read the statement of the ALF, you will see that that's what that says. But the fact of the matter is the data was 16 to 18 drinks, both with the NSAIDs and with the acetaminophen.

CHAIRMAN CANTILENA: Okay. I think that we are clear that we should go back and look at all the data, including that from the earlier hearings. Dr. Kopp?

DR. KOPP: I don't have anything to add.

CHAIRMAN CANTILENA: Okay, and I actually would only want to emphasize I obviously agree that we need to change the label, and I would vote -- I would want to emphasize that we standardize and use some of the improved versions of the label across all of the NSAIDs, because I think that makes sense, and would agree with the couple of points to emphasize the consequences of going over the dosage. I think that's all we'll talk about. So I believe we are finished with GI bleeds.

Is this a comment about GI bleed?

DR. GRIFFIN: Yes. I'm just wondering -- This may just create more problems, but I think that the alcoholics who are at high risk are those who have varices or are at high risk for bleeding or who have

cirrhosis. But other people, like people with ITP or have low platelets, you wouldn't want to put them on an NSAID.

So I'm just wondering if we could resolve it by saying -- you know, creating -- people at high risk of stomach bleeding or other bleeding for other reasons, to make another category. That would include the subgroup of alcoholics that you guys see with varices and uncontrollable vomiting and things like that.

CHAIRMAN CANTILENA: Okay. Let's -- You know, I'm sorry, do you have something else?

DR. GRIFFIN: No.

CHAIRMAN CANTILENA: Okay, sorry. Let's move on to the kidney, and instead of having an open discussion of relative risk, I think perhaps Dr. Kopp, I believe, is a nephrologist, and if I could impose upon you to just sort of give us your impression, if you will, of relative risk in subpopulations, and then we can sort of use that to get us rolling.

DR. KOPP: Okay. Maybe I could say a couple of words about the general renal toxicities of nonsteroidals, and I guess I've listed four. The first would be the acute allergic manifestations, including minimal change disease, interstitial nephritis, that are rare, so rare that we don't really

need to consider them further.

The next would be this hemodynamic and antidiuretic effect where prostaglandins are required to maintain GFR or prostaglandins are required to maintain diuretic activity or, in the case of angiotensin inhibitors, alter the renin angiotensin system.

I guess that's one of the central concerns here, that nonsteroidals and, I believe, to a lesser extent, aspirin, although I have to say I'm not entirely clear on that. Both are felt to compromise prostaglandin synthesis significantly in the glomerulus and in the macula densa.

Maybe I'll come back to special populations in just a minute and say that a third issue is analgesic nephropathy, which is mainly felt to be a combination issue which, hopefully, we are encouraging people to only use a single agent of this class.

But the fourth issue that is also very unclear or very unclear in my mind is the issue of the potentiation of other renal diseases to increase the prevalence of chronic renal failure. I think the handout that we all got gave a good flavor of how difficult this field is, with multiple case controlled studies, that generally most have shown roughly a

twofold increase -- although there are exceptions, a twofold increase of aspirin or acetaminophen or nonsteroidal use in patients who end up on dialysis compared to controls.

Then on the other side, we have two prospective studies, one a smaller one that showed a similar risk, and then more recently the Physician's health study that was also included from JAMA last year that showed no increase incidence of elevated creatinine impaired clearance in 15,000 physicians.

So I think the issue of chronic renal disease is one that is still open, and that comes to the issue, I guess. Traditionally in evaluating drug safety we consider that drugs are guilty until they are proven innocent by appropriate studies. Here, we have the situation where these drugs are being assumed to be innocent, and we are asking is the data sufficient to find them guilty.

Having said that, I guess the two main diseases that we'll be talking about, is there sufficient evidence of guilt to add it to the label, would be this prostaglandin mediated glomerular filtration and diuretic effect, and there I think there clearly is some labeling that needs to be made.

I'm less certain about the issue of chronic renal failure, but at least to get the ball

rolling, I will take the side of saying, yes, I think we need something on the label that at least hints of that issue.

So in terms of special populations, I think what's been laid out here is a proposal. High blood pressure, heart or kidney disease, taking a diuretic or over 65 years of age is an excellent start. I've been wrestling with whether I wanted to add liver disease to that.

The argument for would be to try to capture those patients that particularly, if we take alcohol off, would be at risk, people with cirrhosis who again depend on prostaglandin E-2 to maintain their GFR.

There is a downside to adding chronic liver disease, which is that many patients know that they have liver disease from hepatitis C or B, and yet they don't at this point have cirrhosis, and so will we be capturing by that proposal more patients than we wish to exclude?

Of course, we could also say serious liver disease, but that begs the question, how serious in the patient's mind does it have to be? But anyway, as a first draft, I guess I would include heart, liver or kidney disease, and I guess I'll stop there for now.

CHAIRMAN CANTILENA: Okay. Does anyone have any challenges to that as a starting position or differing views. I think that's the way we will handle that, and then we will actually vote.

DR. NEILL: I'd just like some clarification about whether these subpopulations are at risk for using OTC doses at OTC durations of treatment. The heart failure, I could see, but I want you to comment about that specifically.

DR. KOPP: Yes, I believe the answer is probably yes. In part, I am being guided by that NKF symposium that was put together about five years ago now, and I would believe that that is the case for ibuprofen.

I would have to say that I'm not sure I can quote the papers chapter and verse for aspirin in conventional doses for the same indications. Does that answer?

DR. CRYER: May I also chime in?

CHAIRMAN CANTILENA: Yes, Dr. Cryer. And actually, the assumption is at OTC on the labeling doses. It's not overdose or exceeding.

DR. CRYER: Right. That was the point I just wanted to further explore whether your opinions would be modified by the data that we saw today. I think there was one. Dr. Griffin showed us the data

that, at least the OTC doses of ibuprofen, the 1200 milligrams and less range, I believe, that the risk was actually -- the relative risk was actually .9. So no increase in the renal effects.

Then the data that the sponsors provided us, we specifically queried them on this issue, and at OTC doses of ibuprofen they didn't express any experience of having any of these renal issues that are certainly of concern at the prescribed doses of NSAIDs.

CHAIRMAN CANTILENA: Dr. Johnson, you had a comment?

DR. JOHNSON; I'm particularly concerned about adding labeling relative to heart failure, because that's a population I deal with a lot. I think that it's probably true that we don't have overwhelming evidence that OTC doses are a problem, but I think we also know that patients take sometimes larger than OTC doses, and I think the problem in heart failure, unlike hypertension where, if it's intermittent use, it may be sort of small levels of blood pressure elevation, and that might not be a big deal.

In heart failure we are talking about sort of tipping the balance in the wrong direction, and a couple of days of even 400 milligrams three times a

day -- I'm not convinced that that's not enough to put a sort of right on the edge heart failure patient into decompensated heart failure and into the hospital.

So I guess this is one of the areas where I feel everything we know about that patient population and about the effects of this drug class supports that that occurs, and the fact that we don't have controlled trial literature documenting that doesn't bother me.

I believe, in terms of aspirin, the evidence of those effects is that it is at much, much higher doses. I'm not sure that it is that you see those effects at OTC doses. So I'm struggling a little bit about that labeling on aspirin as opposed to the NSAIDs. I feel pretty strongly about that for the NSAIDs.

DR. KOPP: Maybe I could get a clarification from Dr. Griffin. I was thinking about the acute renal failure data that you showed, that overall the risk was 1.58, and then the risk for ibuprofen was actually higher. Is that what you are referring to or is it something else?

DR. GRIFFIN; In my data the risk for ibuprofen was lower. It was a subgroup analysis. Overall, you're right, it was 1.58 for acute renal failure, and for ibuprofen, when we were able to look

at it on a dose response, because most of our use was ibuprofen, and we found that the higher dose was associated with a higher risk.

In a 1200 milligram dose we could not detect an increased risk of acute renal failure at that dose. Now I think other people have detected elevations in blood pressure at that dose. So there obviously is a renal effect, but we didn't detect any acute renal failure excess at that dose.

DR. KOPP: Well, I guess another way of looking at it is we are not denying this drug to those patients, simply say take it in the context of physician's care rather than on your own.

CHAIRMAN CANTILENA: Okay. Why don't we -- unless I hear a crying need for further discussion on this, I think one way to expeditiously handle this is to basically vote with a show of hands whether or not we feel that the label should be altered to include issues concerning the kidney and nonsteroidals or aspirin.

We could say that it will be yes or no, that it should be altered, and then we will list -- I guess I have -- Dr. Kopp, please correct me if I'm wrong. Kidney disease, use of a diuretic, heart failure were three that I caught for sure, and I guess you weren't sure of liver disease.

How about if we split it out for the first three. So the first vote --

DR. CRYER: This is an important issue. The current proposal for ibuprofen has those issues. So it says ask your doctor before use if you have high blood pressure, heart or kidney disease, are taking a diuretic, or are 65 years of age or over.

So are you suggesting --

CHAIRMAN CANTILENA: What page are you on, because I have --

DR. CRYER: This is the proposed label. It's the second to last page, label F.

CHAIRMAN CANTILENA: Okay, I have the ibuprofen 200. Okay. This one just says proposed in the upper right?

DR. CRYER: Right.

DR. KOPP: Yes, that's what I was taking as my working start. Could I also make one other point? At some point I would like to discuss the idea about prolonged use and a statement about that. Do you want to do that now or do you want that --

CHAIRMAN CANTILENA: Yes. I think our sort of initial round on the kidney will involve just the limits of the OTC label. Okay. So Dr. Cryer, what was your point again? I'm sorry.

DR. CRYER: Well, are you suggesting a

revision to this proposal or what are we revising?

CHAIRMAN CANTILENA: It was my understanding that Dr. Kopp wanted to strengthen three specific areas, and I guess, if we look at it, we'll have to decide whether or not we think these areas should be strengthened. You are saying that --

DR. CRYER: I'm saying that all of the areas that he suggested strengthening are currently captured in the proposed label, as I see it.

CHAIRMAN CANTILENA: Right. So --

DR. KOPP: I would agree, with the one additional thing about liver disease.

CHAIRMAN CANTILENA: Right. So your vote in that case, as we separate out the three, would be no.

DR. BRASS: MR. Chairman, could I make a suggestion?

CHAIRMAN CANTILENA: Sure, Dr. Brass.

DR. BRASS: I think the multiple labels being distributed may be causing some confusion, and rather than talking about change or keeping the same, I think we might simply convey points we want to be sure are made effectively in whatever label is made. I'm sure the agency can then integrate into their proposed rulemaking.

CHAIRMAN CANTILENA: The problem with that

is that we would end up going around, and everyone could have their own sort of version, and then half of the committee will be gone, you know, in terms of flights at the airport.

DR. BRASS: Well, again I think we could take those issues as ones we want to be sure are conveyed, whether this label is adequate or not. Naturally, nobody knows. We haven't tested anything.

CHAIRMAN CANTILENA: Right. I guess my point was, if you are working from the proposed label, we want to make sure that we are comfortable that we are at least hitting the things that we feel are relevant and important. So that, really, the question would be -- and Dr. Kopp, I believe you were saying that those three areas at least you thought were not emphasized well enough, suggesting --

DR, KOPP: They are emphasized well in the proposed labeling.

CHAIRMAN CANTILENA: Okay, that's the part that I wasn't --

DR, KOPP: So I'm happy with the proposed label. For now, I'll say let's add liver disease to that.

CHAIRMAN CANTILENA: Okay. So let's say, is there anyone who disagrees that these are three important items and would support the proposed label

as it is, as sufficient for emphasis of these three areas?

DR. BRASS: All I would say is, again, I'm a little bit uncomfortable, because rather than endorsing a specific label, we have no data to say whether this is the best way to convey these concerns, and whether heart disease is the same as heart failure to everybody, whether having the specific versus the general.

I think the concepts, I agree completely with. Whether I think this is the best way to do it or not, I really don't know.

CHAIRMAN CANTILENA: Okay. So would we -- I guess, Dr. Ganley, is it sufficient for us to recommend that these three areas be adequately highlighted and that the label then -- that your group will have this label evaluated prior to implementation so that our concerns that these areas are sufficiently highlighted will be met?

DR. GANLEY: Right. I think the one thing I just want to mention is -- and I don't mean not to endorse validating things. But I think you have to understand the position that we are in.

It's not -- We don't have much of a stick in that regard, because someone could keep doing -- We could put it in the label however we want, and they

could do some label comprehension study and say, oh, doesn't show it, can't convey that message.

So, you know, I understand what you are trying to say, and we are going to have to figure out something from a regulatory point of view that encourages studies to be done on these things, but if we want all this information in, and the only way we can get it in is if someone gives us valid data that supports that it tells something to someone, well, we're never going to get it in, because no one is going to ever give us valid data.

So I'm just throwing that out there. I understand what you're saying, and we just need to figure out from a regulatory point of view how to use a stick to make it work. Okay. But you know, you're throwing in the valid data. Well, we're not going to see valid data, if that's the requirement that's thrown on top of us, because --

CHAIRMAN CANTILENA: Well, I think the other way to handle this is to look at the existing label and say it's inadequate. That would be another option to get the same message across.

DR. GANLEY: But what am I going to do, take these drugs off the market because they don't have valid labels? How can I force someone to do a study if -- You know, I understand what you are

saying, and we will figure out a way to make it work, but I just want you to understand that, to say that the only way you can put this on a label is if we get valid data that supports that it conveys the message, well, I can tell you, the likelihood of us getting valid data is slim and none.

You can do a lousy study and show we can't convey that message.

DR. BRASS: No, my point was that, again, there's been a lot of, I think, really good ideas come out of the discussion, and you have heard those. For us to sit here on the fly and try to integrate those into an optimal document is probably not as useful as you hearing those important concepts and you applying your judgment and experience and what data is available to integrate them into the optimal label.

CHAIRMAN CANTILENA: It may come out that we have to make up a label that we think looks pretty good. We won't have a label comprehension study to prove that it conveys the message, but the burden then is on industry to tell us that we are wrong, and we can do it a better way, I think. But to say that we have to validate that it conveys the message is a burden that we would never be able to achieve.

DR. BRASS: Yeah, but again you have lots of data in a variety of contexts that you can call

upon to extrapolate and make informed judgments.

CHAIRMAN CANTILENA: I think -- I mean, you know, these are your questions, and we are trying to answer them, and I guess I'm actually struggling with how to answer the question in a way that you can use the information; because now you are saying, if we say change or go with the proposed if validated, you can't do that.

So at the risk of staying here, Dr. Johnson, one more comment, and then we are going to come to resolution on this.

DR. JOHNSON: I would just like to make an argument for the wording "heart failure" rather than heart disease, because heart disease includes post-MI patients, and we don't want post-MI patients not using aspirin. I'm not sure all heart failure patients would pick themselves up under heart disease, but I think they would pick themselves up under heart failure.

So I think -- In general, I agree, but I think it should say heart failure and not heart disease.

CHAIRMAN CANTILENA: Okay. Dr. Ganley, in order to try to answer sort of for you question 2(b) and question -- Well, actually really tied into also 1(d) -- would it help you if we voted on the three

most important areas that we feel should be conveyed so that you had at least a sense of the entire panel in terms of what the areas were that we thought would be most important, or would you prefer that we open it up for comments, and we continue the comments that we've had to highlight anything in terms of additionally, and we'll use the proposed label as our foundation, anything in terms of any extra either subpopulations as they relate to changing the label.

It's actually your choice, because we're sort of at an impasse.

DR. JENKINS: I would just suggest that you follow the same approach that you followed for question 2(a). You put the question to the committee of whether labeling changes were needed, and you took a yes/no vote, but then you asked people to comment on what those changes might be.

I think it would be helpful for us if you are consistent in how you approach these two separate risk factors and not now try to have up/down votes on specific renal toxicity wording, when you didn't do that for the GI, and I would hate for us to have to go back and do all those GI points that you mentioned.

CHAIRMAN CANTILENA: Okay. Then let's follow that lead, and I know some of you are looking at the watch for your flight times. Let's try to help

this along. Let's go with the Kopp list. And Dr. Kopp, if I could use your, I guess, four items, and if you wish to drop the liver, you can, but the items on the Dr. Kopp list are kidney disease, use of a diuretic, heart failure, liver disease.

So if you vote that, yes, additional warnings should be added above and beyond the proposed label, this will be our foundation. This is our anchor. Then you can accept the Kopp as a block or you can modify.

DR. KOPP: Did you have high blood pressure on there?

CHAIRMAN CANTILENA: Pardon me?

DR. KOPP: High blood pressure should be on there. So five elements.

CHAIRMAN CANTILENA: It's already there, but I'm talking about in terms of accepting the recommendation, if we think that we need to modify this to further emphasize or change, add warnings to emphasize this, we can say, yes, all of these things should be emphasized and, for example, the warning for heart failure should be highlighted, etcetera, etcetera; or if you are comfortable with the fact that we have them all in the proposed label and you are comfortable with the strength of the message without testing, just as it sits, in your opinion, then we can

just go forward. Okay?

Does anyone have any questions about the ground rules? Dr. D'Agostino?

DR. D'AGOSTINO: Are we splitting ibuprofen from aspirin? Is it two separate votes?

CHAIRMAN CANTILENA: Dr. Ganley, are we splitting aspirin?

DR. GANLEY: Yes, you are.

CHAIRMAN CANTILENA: Okay. Dr. Clapp just has one question for the hepatologists about liver disease.

DR. CLAPP: I would just like your insights on the need to put the broad category, liver disease, for an ibuprofen warning.

DR. WATKINS: I can comment on that. I think, you know, depending on how you define it, there are tens of millions of people with liver disease, and I would think liver cirrhosis would be the right term. I think, actually, most people have some concept of what cirrhosis is, but even if they don't, they are at least asking the right question of their doctor or pharmacist: Do I have liver cirrhosis rather than liver disease?

So I would suggest, just as with heart failure versus heart disease, it would be liver cirrhosis rather than liver disease.

DR. CLAPP: So, Dr. Cantilena, would you be amenable to altering it to cirrhosis or no? I mean, it just sounds so broad. Liver disease is --

CHAIRMAN CANTILENA: Yes. I think we would have an issue, probably, with the understanding for the average consumer if we got specific. But if your recommendation is that it should be disease specific, using that word --

DR. CLAPP: I would ask the hepatologists to make a recommendation.

CHAIRMAN CANTILENA: I think they will as we go around the table. So, Dr. Jenkins, you want it for aspirin and then for other nonaspirin NSAIDs. Okay. Are you leaving?

DR. CUSH: Yes, I am. And my vote would be the label should be changed. The label should say that there should be a warning for patients with kidney failure, for problems with kidney function, heart failure and diuretics, only.

CHAIRMAN CANTILENA: And the same for aspirin and nonaspirin?

DR. CUSH: The same for aspirin and ibuprofen and all of --

CHAIRMAN CANTILENA: Okay.

DR. CRAWFORD: Clarification, please?

CHAIRMAN CANTILENA: Sure.

DR. CRAWFORD: Dr. Kopp, did your recommendations include aspirin and the other NSAIDs?

DR. KOPP: That is a good question, and I'm not sure that I have gone over the data nor seen it presented to have a firm understanding about the effects of OTC levels of aspirin on that. So it's a hedge.

CHAIRMAN CANTILENA: Okay. So that's the hedge. So let's just get on the same page. We are using the proposed label for ibuprofen as the, quote, "model" for the nonaspirin, nonsteroidals, and that would be found in Appendix F. Then we are using the aspirin label for the aspirin consideration of this question, and that would be found under Section B as in Boy, B as in Boy.

All right. Let's start -- Actually, let's start with Dr. Kopp. First, give me your answer for ibuprofen, and then your answer for aspirin. The question is: Should changes be made to these labels, as specified, and if so, should they include the five items or exactly how would you like to handle it? Do it first for ibuprofen and then second for aspirin.

DR. KOPP: So for ibuprofen, I would say high blood pressure, heart failure, liver cirrhosis or kidney disease or taking a diuretic.

CHAIRMAN CANTILENA: Okay. And aspirin?

DR. KOPP: Aspirin -- As I say, I have less confidence in what to say. I guess as a first draft, I'll say the same.

CHAIRMAN CANTILENA: Okay. Dr. Rumack?

DR. RUMACK: On the absence of other data, I will echo Dr. Kopp.

CHAIRMAN CANTILENA: Dr. Crawford?

DR. CRAWFORD: For the ibuprofen, I concur. For the aspirin, I abstain.

CHAIRMAN CANTILENA: Thank you. We have Dr. Cush's thought. Dr. Elashoff?

DR. ELASHOFF: I abstain on both.

CHAIRMAN CANTILENA: Dr. Watkins.

DR. WATKINS: I concur on the ibuprofen but abstain on the aspirin.

CHAIRMAN CANTILENA: Dr. Brass?

DR. BRASS: I agree with the populations identified, though as I earlier indicated, I am actually a little bit less concerned about hypertension from a clinical standpoint. The issue of misuse is addressed by our previous comments, which I actually still think is the most important, to limit use to the duration.

I believe aspirin has less effect than ibuprofen, but I cannot differentiate it in this dose range. So I would default to having the same language

for aspirin as ibuprofen.

CHAIRMAN CANTILENA: Dr. Davidoff?

DR. DAVIDOFF: I would also say yes to both, to the list of five for both ibuprofen and aspirin, partly because the instruction is not to not use the drug. It's to ask a doctor before use, which seems to me to be entirely prudent and reasonable guidance, particularly since even though, strictly speaking, this is directed at OTC dose usage, it's very clear that there are other uses. It's used well beyond that by many people.

CHAIRMAN CANTILENA: Dr. Lam.

DR. LAM: Yes for ibuprofen, and I abstain for the aspirin.

CHAIRMAN CANTILENA: Dr. Cryer.

DR. CRYER: Yes to both.

CHAIRMAN CANTILENA: Dr. Laine?

DR. LAINE: Yes to both.

CHAIRMAN CANTILENA: Dr. D'Agostino?

DR. D'AGOSTINO: Yes to ibuprofen, abstain on the aspirin.

CHAIRMAN CANTILENA: Comments from Dr. Alfano?

DR. ALFANO: No comments on this one.

CHAIRMAN CANTILENA: Dr. Clapp?

DR. CLAPP: Yes to ibuprofen, but with the

elimination of the liver disease as an "ask the doctor," and yes to aspirin.

CHAIRMAN CANTILENA: Dr. Katz?

DR. KATZ: I agree with the recommendations for ibuprofen. I favor stronger language for patients with history of stomach ulcers. As I had mentioned earlier, rather than asking for use, do not use without being under a doctor's supervision. And I will abstain from the aspirin.

CHAIRMAN CANTILENA: Dr. Williams.

DR. WILLIAMS: Yes to both.

CHAIRMAN CANTILENA: Dr. Neill.

DR. NEILL: Yes to both.

CHAIRMAN CANTILENA: Dr. Patten.

DR. PATTEN: Yes to both.

CHAIRMAN CANTILENA: Dr. Day?

DR. DAY: Yes to ibuprofen. Abstain for aspirin.

CHAIRMAN CANTILENA: Dr. Cohen.

DR. COHEN: Yes to both.

CHAIRMAN CANTILENA: Comment from Dr. Griffin?

DR. GRIFFIN: Yes to ibuprofen, no to aspirin.

CHAIRMAN CANTILENA: Okay. Thank you. Let's move now to item 3, which we have already

partially covered, and Item 3 is concerning the professional labeling which you have in front of you. The question again s with the labeling, and we will just go yes/no --

DR. GANLEY; Lou, I'm not sure we need to go over it, because we already want some gastrointestinal and some renal stuff. So I think it would be just a redundant discussion.

CHAIRMAN CANTILENA: Okay, so you've already been advised on Item 3. Correct?

DR. GANLEY: Yes.

DR. JENKINS: Yes, I think so. As I said earlier, if a sponsor or someone wants to make the proposals that those indications be actually over-the-counter indications, we would need them to put together the data in the same way that you would do normally for an NDA over-the-counter switch or it could be in the form of a citizen position.

I would remind the committee that we had a couple of meetings not that long ago about prophylactic use or the use of the statin drugs for the prevention of cardiovascular disease, and while those drugs have not been approved, we have considered those as possible over-the-counter indications.

It may be the time that the committee may want to voice your opinion of whether it's time to

consider the cardiovascular indications for aspirin for inclusion on the over-the-counter label. That's going to need to be data driven. There's going to be a lot of need for discussion and serious consideration of that, but maybe times have changed.

CHAIRMAN CANTILENA: Yes, I think you've framed the issue, and I would actually say that, if a sponsor chooses to go down that, we would certainly look forward to that meeting. Dr. Kopp?

DR. KOPP: Could I go back to question 2 for a minute, and this is an idea that I think at least Dr. Davidoff and maybe others have raised before. Should there be some additional statement addressing the issue that many patients are taking this chronically, every day of their lives, even though that's not part of the OTC label, and some statement along the lines of the prolonged regular use of NSAIDs may increase your risk of gastrointestinal or kidney disease, to at least alert people that there are additional issues that have to do with regular use as compared to a ten-day limit.

CHAIRMAN CANTILENA: Yes, I think that's a good point, and actually, Dr. Titus just reminded me that I did not vote in all the excitement on question number 2.

So I actually vote yes to both for the

reasons actually stated by either Dr. Cryer or Dr. Brass in terms of the similarities and probably small differences that exist, if indeed any exist.

Okay. Number 4 should be very straightforward. Are any additional studies important or are they required to evaluate the issues further, and then evaluation of the labeling. We have talked about this, studies to evaluate subpopulations.

I think we have already touched on this, and I would ask the members if there are additional issues that we have not mentioned. I realize that we have lost about a third of the committee. The numbers are dwindling, but for those here, are there any additional studies, any subpopulations that you would like to see evaluated, realizing that Dr. Ganley just can't pick up the phone and order these studies, but perhaps he can partner with the NIH to stimulate the NIH to actually study these.

So any specific areas that you would like addressed? Dr. D'Agostino.

DR. D'AGOSTINO: Just to go back to the label comprehension, I think that we as a committee or consultants to the committee with a voting right should emphasize to the sponsor and to the FDA that we do think label comprehension is very important, and those studies should be done, and the FDA shouldn't be

held captive, that they have to somehow or other come up positive. I mean, these things really need to be done, and we don't want to leave it with the notion that, because there might some sort of a way out for the sponsor, that we'll drop the need.

CHAIRMAN CANTILENA: Right. And I would also sort of urge the sponsors, certainly under the monograph, if they have information or they are going to be doing a study, this should be submitted to the FDA so they can evaluate it, so that when we are in a situation such as we were this morning, we can have the information. We can examine the study, and we can evaluate quality of the information.

Dr. Brass?

DR. BRASS: I would again make the same comment I made yesterday afternoon, that we are in desperate need for research on risk management techniques in the OTC population. This is just another example. And again the other theme is that, while we have developed very good, large cross-sectional and prospective and all other kinds of data for the general population, we all remain concerned about populations at risk.

Studies that explore and challenge the safety and appropriate use in those at risk populations would have clearly made our decision

making easier, and I think would guide future decision makers if those kind of studies were available.

CHAIRMAN CANTILENA: Yes, Dr. Davidoff.

DR. DAVIDOFF: Yes. On this very sort of confusing issue of alcohol and NSAIDs, I wonder if it wouldn't be appropriate, not so much to ask for new studies, but to go back down and dig into the literature on the issue not of the contribution of NSAIDs and aspirin to incidence of bleeding, but to outcome of bleeding; because it seems to me there probably are such data, almost certainly not from any sort of randomized intervention trials, but from various other kinds of observational studies.

It seems to me that would be extremely helpful in deciding whether or not it does make sense to keep some sort of alcohol warning on the label, and those data probably are -- The answer is out there probably, and it would be helpful to have that.

CHAIRMAN CANTILENA: Dr. Day, then Dr. Patten.

DR. DAY: Just a comment about ways to enhance people's ability to read and understand the information. There are peel-back labels that can be put directly on bottles, not so much to increase the amount of information we put on. You can slip in a couple more things, but you can make the print larger,

and I know this is expense from the manufacturing standpoint, but by peeling back, you can then enhance the size.

So if you had a square that was this big, it will now be -- Let's see. It will be one, two, three or four times bigger. Now the problem with that is I have observed in market research that people don't see that you are supposed to peel it off. So they don't do it. So there's ways to enhance that corner on the bottom with the various techniques so that they will do it.

So I just am hesitant about leaving out something that we think is really important just because we don't want to have too many things on. So I think that we need to reexplore these ways to extend not the amount of information but the accessibility of it.

CHAIRMAN CANTILENA: Dr. Patten.

DR. PATTEN; I would ask a question regarding research having to do with the transmission of all of these pain relievers in breast milk. I don't know if that research has been conducted. If it hasn't, perhaps it should be, and we might want to think of nursing infants as a subpopulation.

CHAIRMAN CANTILENA: It has for a lot of them, I know. That's available in the literature.

We've asked the FDA just to help us with question 5. Are we done with question 4? Any further studies, any further ideas? Dr. Jenkins, do you have a comment?

DR. JENKINS: About question 5.

CHAIRMAN CANTILENA: Okay. Actually, I have asked Dr. Ganley's staff to scan a few labels in, just like we did yesterday for the acetaminophen, just to show the panel sort of what the current state of affairs is.

DR. GANLEY: I'm not sure we need to go into that. I think -- After hearing everything today, I'm not sure why many of the comments yesterday weren't carried over today in terms of prominent labeling on the packages, things like that. So I'm not sure, you know, it's worthwhile pursuing that right now.

DR. JENKINS: I would agree. I think the committee has made pretty clear that you would like to make sure that the active ingredient is very prominently displayed and readily accessible and that there would be instructions not to use two drugs in the same class.

So I'm not sure -- unless you have other comments, I don't think you need to go into a specific discussion of this.

CHAIRMAN CANTILENA: Okay. Did Dr. Cohen

have a comment?

DR. COHEN: Yes. I just wanted to reiterate the idea of using the term NSAIDs to identify NSAIDs, etcetera. That would also help with allergy recognition. Obviously, that could be -- With anaphylaxis, that could be fatal, and it's immediate and no time to react. So people need to see that right away.

The other idea we talked about a little bit earlier was the idea of a patient leaflet, and I think that's a great idea to be able to communicate information.

It also gives you the ability to tell people what might happen if they don't heed a certain warning, and I think that would help with people following the advice on the label.

So I think that's something that could be very useful. Also, in taking some of that information that isn't so important and placing it in the leaflet, it would allow you to have that -- you know, less is more on the immediate carton - or the carton and also the immediate package label.

CHAIRMAN CANTILENA: Okay, thank you. Dr. Elashoff, then Dr. Clapp.

DR. ELASHOFF: Nobody has mentioned so far using the Web as an educational tool, and there you

can easily expand the information quite a bit and even essentially search on words that you are interested in. I think all of the manufacturers should be encouraged to have a really informative Website.

DR. CLAPP: I'd like to have the opportunity to express a concern about pediatric dosing to the FDA and manufacturers, and once again that is about the ambiguity of dosage mechanisms for children.

We are talking about ibuprofen today. for ibuprofen drops, the measuring dispenser for the drops is 1.25 milliliters, and the concentration is 50 milligrams per 1.25 milliliters. A teaspoon or 5 milliliters of ibuprofen suspension is 100 milliliters.

Now the unfortunate thing -- and I'm happy to see that McNeil has made a chart, but disappointed to see that they are causing some of the schizophrenia in dosing, because with Tylenol drops the milliliter -- the dispensing mechanism is .8 on the dropper.

For parents who buy ibuprofen, their brand being Motrin drops, the Motrin drops are 1.25 per dropper. Now parents -- and some people say they don't get phone calls. I get phone calls about what drops to use at what time, all times of night also, and I have to clarify with them what drop are they

using.

I lost the one dropper, and my dropper says 1.25. These people are going to use it with the wrong product. If you do the math, if you use an ibuprofen dropper for a Tylenol drop product, you can have an overdose going every four hours for an 11 kilogram child of about 100 milligrams per kilogram per day, and yesterday the dosage was told to us, the toxic is 125.

I don't know 100 will do something to you if you are a dehydrated person. We were hearing about problems with pre-renal failure in children who are dehydrated.

This just, once again, illustrates that standardization of dosing is imperative in children, and people who are laypeople and even professionals, when they get droppers, they think all droppers are equal.

So I am imploring manufacturers as well as the FDA to put some standardization to the concentration of the drops in terms of milligrams per milliliter, and standardization of the designated measurement in the drops.

CHAIRMAN CANTILENA: All in favor of having that as a recommendation from the committee, say Aye or raise your hand. Raise your hand. We need

a little exercise. Any opposed? Any abstain? I'm sorry. Dr. Rumack, are you opposed?

DR. RUMACK: I voted yes, but I had a follow-up comment on that. In 1999 we worked on the dosage in pediatrics and taking it down to a lower level. I know Dr. Ganley said yesterday there was some concern between two and six months of age.

The fact of the matter is that we start -- As pediatricians we begin immunizations at two months of age, and the first thing you tell the parent is, if you go home tonight and your child is irritable or cranky or whatever, give them some Tylenol, and you end up with no dose on the bottle. So they guess.

I think it would be very useful, with whatever prohibitions we want to have on there, to have a dosing between two months and two years of age, because that is the reality of what we are giving in practice.

There's many, many pediatricians that are doing that every single day. So I understand your thought about bacteremia and so forth, although that really peaks at about 30 days of age.

DR. GANLEY: And we've done an extensive review of the literature. It's in the rulemaking, and I think it's clear that there is some concern between two and six months of age where children who develop

fevers -- they need to call their pediatrician to make sure that they don't have some other serious condition.

You can write your comment to the rulemaking when it comes out. But I think the literature is clear, and many of the recommendations out there that we see suggest it could be down to six months of age. But you are welcome to, you know, send a comment in.

DR. RUMACK; You know, maybe we need to distinguish between development of fever and the administration of it for following immunizations, because I can tell you, virtually every pediatrician is telling their patients at two months and at four months and then again at six --

DR. GANLEY: Right, and so they tell them, take this dose. So they're telling them take acetaminophen at this dose after the immunization, if you need it. Again, we can -- You can discuss it in the rulemaking.

CHAIRMAN CANTILENA: Okay, I just had one more, actually, question. Yesterday the committee was on the verge of a recommendation that be transmitted to the FTC concerning marketing and advertising. I think I understand it.

Dr. Jenkins has some information about how

that might happen, if it could happen, etcetera.

DR. JENKINS: Yes. Well, actually, yesterday there was some discussion, and we weren't able to give you a clear answer, on the basis for the separation of authority between over-the-counter drug advertising oversight by the Federal Trade Commission versus prescription drug oversight by the Food and Drug Administration.

It is -- As we suspected, it is statutory in its basis, and the history that we have been able to dig up from my staff back at the office is that in 1938 Congress, by law, made the Federal Trade Commission responsible for all drug advertising, but then in 1962 with the amendments to the Food, Drug and Cosmetic Act, they gave FDA responsibility for advertising of prescription drugs.

So it is statutory in its basis. So some of the suggestions yesterday that the responsibility be shifted form one organization to the other would require statutory changes, which would be in the purview of Congress.

CHAIRMAN CANTILENA: Right, and if I recall, Dr. Cush's comment was we will start lobbying with you, and we'll work our way up. So I think that would be something that I would see as an advantage for consistency.

Are there any other issues, Dr. Ganley, Dr. Jenkins, that we have not touched on? Any other issues from the committee members?

Then at approximately 4:20, we are adjourned. Thank you very much. Thank you to the speakers and those remaining committee members.

(Whereupon, the foregoing matter went off the record at 4:20 p.m.)