UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

+ + +

CENTER FOR DRUG EVALUATION AND RESEARCH

+ + +

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

+ + +

SAFETY ISSUES RELATED TO

ACETAMINOPHEN

+ + +

MEETING

+ + +

THURSDAY,

SEPTEMBER 19, 2002

+ + +

The Advisory Committee meeting was held in the Maryland Ballroom, Hilton Silver spring Hotel, 8727 Colesville Road, Silver Spring, Maryland, at 8:00 a.m., Louis Cantilena, M.D., Ph.D., Chairman, presiding.

PRESENT:

LOUIS CANTILENA, M.D., Ph.D., Chairman

SANDRA TITUS, Ph.D., Executive Secretary

LESLIE CLAPP, M.D., Member

PRESENT (Continued):

FRANK F. DAVIDOFF, M.D., Member

JULIE A. JOHNSON, Pharm.D., Member

Y.W. FRANCIS LAM, Pharm.D., Member

SONIA PATTEN, Ph.D., Member/Consumer Representative

DONALD L. UDEN, Pharm.D., Member

HENRY W. WILLIAMS, JR., M.D., Member

ALASTAIR WOOD, M.D., Member/Consumer Representative

SGEs PRESENT:

ERIC BRASS, M.D., Ph.D.

MICHAEL COHEN, R.Ph., M.S., D.SC.

STEPHANIE Y. CRAWFORD, Ph.D.

BYRON CRYER, M.D.

JOHN CUSH, M.D.

RALPH D'AGOSTINO, Ph.D.

RUTH S. DAY, Ph.D.

JANET ELASHOFF, Ph.D.

CURT DANIEL FURBERG, M.D., Ph.D.

NATHANIEL KATZ, M.D.

LOREN LAINE, M.D.

RICHARD NEILL, M.D.

PAUL B. WATKINS, M.D.

H. JAMES WILLIAMS, M.D.

MICHAEL C. ALFANO, D.M.D., Ph.D. (Non-voting)

WILLIAM LEE, M.D. (Non-voting)

FDA MEMBERS PRESENT:

RIZWAN AHMAN, M.D., M.P.H.

JULIE BEITZ, M.D.

JONCA BULL, M.D.

STEVE GALSON

CHARLES GANLEY, M.D.

WILLIAM GILBERTSON, Pharm.D.

JOHN JENKINS

DEBBIE LUMPKINS

PARIVASH NOURJAH, Ph.D.

JOHN SENIOR, M.D.

ALSO PRESENT:

DEBRA BOWEN, M.D.

SHERYL JENKINS

RAYMOND S. KOFF, M.D.

JOHN SLATTERY, Ph.D.

ANTHONY R. TEMPLE, M.D.

STEPHEN COOPER, M.D.

JOHN DENT, M.D.

ALLEN HELLER, M.D.

RAY BULLMAN

PAUL DAUGHIN, M.D.

SARAH ERUSH, Pharm. D.

MS. KATE

LOUIS LASAGNA, M.D.

ALSO PRESENT (Continued):

PETER LURIE, M.D., M.P.H.

CAROLINE RIELY, M.D.

SUSAN WINCKLER

C-O-N-T-E-N-T-S

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

(8:04 a.m.)

CHAIRMAN CANTILENA: Welcome to the September 19th meeting of the Nonprescription Drugs Advisory Committee, here to discuss issues concerning acetaminophen safety.

My name is Dr. Lou Cantilena. I'm the head of clinical pharmacology at the Uniformed Services University, and I'll be chairing this session today.

What we'd like to do is to go around the table and have everyone introduce themselves, and we'll start over on this side, please. Sir, if you can introduce yourself.

DR. FURBERG: Curt Furberg, Wake Forest University.

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

DR. CUSH: Jack Cush. I'm a rheumatologist from Presbyterian Hospital, Dallas.

DR. ELASHOFF: Janet Elashoff, biostatistics, UCLA and Cedars-Sinai.

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

DR. BRASS: Eric Brass, Harbor UCLA

Medical Center.

DR. DAVIDOFF: Frank Davidoff, the editor emeritus of Annals of Internal Medicine.

DR. LAM: Francis Lam, University of Texas, Health Science Center in San Antonio.

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

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

DR. D'AGOSTINO: Ralph D'Agostino, biostatistician from Boston University and the Framingham study.

DR. ALFANO: Mike Alfano, New York University.

DR. CLAPP: Leslie Clapp, pediatrician, Main Pediatrics and Clinical Associate Professor, State University of Buffalo.

DR. TITUS: Sandy Titus, FDA. I'm the Administrator for the Nonprescription Drugs Advisory Committee.

DR. JOHNSON: Julie Johnson, University of Florida.

DR. JAMES WILLIAMS: Jim Williams,

rheumatologist at the University of Utah.

DR. UDEN: Don Uden, University of Minnesota.

DR. HENRY WILLIAMS: Henry Williams, family practice, Howard University, Washington, D.C.

DR. NEILL: Richard Neill, family practice, University of Pennsylvania.

DR. PATTEN: Sonia Patten. I'm an anthropologist from Minneapolis, Minnesota, and I'm one of the consumer representatives.

DR. WOOD: I'm Alastair Wood, and I'm a clinical pharmacologist from Vanderbilt.

DR. DAY: Ruth Day. I do research on medical cognition. I'm at Duke University.

DR. COHEN: Mike Cohen from the Institute for Safe Medication Practices.

DR. BEITZ: Julie Beitz, Director, Division of Drug Risk Evaluation in CDER, FDA.

DR. GANLEY: Charlie Ganley, Director of OTC Drugs, FDA.

DR. BULL: Jonca Bull, Director, Office of Drug Evaluation V, and the Center for Drug Evaluation and Research.

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

MR. GALSON: Steve Galson, Deputy Director of the Center for Drug Evaluation and Research.

CHAIRMAN CANTILENA: Okay. Thank you, everyone.

We will now hear the conflict of interest statement from Sandy 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 discussion. This includes: Drs. Byron Cryer, John Cush, Sonia Patten, Eric Brass, Ralph D'Agostino, Ruth Day, Curt Furberg, 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 meetings are issues of broad applicability. Unlike issues before committee in which a particular product is discussed, issues of broad applicability involve many industrial

sponsors and academic institutions.

The committee members and 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 industry 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 discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants' involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any

firm whose products they may wish to comment upon.

Thank you.

CHAIRMAN CANTILENA: Thank you, Dr. Titus.

I will now ask Dr. Charles Ganley to start us off.

DR. GANLEY: Good morning. I would like to start by taking the opportunity to thank all of the members of the Advisory Committee and the consultants to the committee who are taking time from their busy schedules to participate in today's meeting.

There are four things that I'm going to touch on this morning to introduce the discussion over the next two days.

First, many members of today's committee have not previously been involved with Advisory Committees addressing OTC drug issues. So I'm going to give a brief overview of how over-the-counter drug products are regulated and a brief history of the OTC drug review.

Second, I hope to explain why I bring these issues today and tomorrow.

Third, I'm going to make some comments about safety and efficacy of internal analgesic drug products.

And last, I want to give some brief

comments on today's topic for discussion: unintentional acetaminophen overdose.

Over-the-counter drug products can be marketed under two different regulatory mechanisms, either through drug monographs under the OTC drug review or under new drug applications.

When marketing under a drug monograph, the manufacturer follows the condition of views provided for in the monograph. The drug monographs are categorized by the indication's pharmacologic effect and body system affected.

There are no regulatory requirements mandating that manufacturers provide information on a specific product, such as manufacturing process or adverse event reports to the FDA. The FDA can, however, expect manufacturers to obtain information or the manufacturer can voluntarily provide information if asked.

Drugs marketed OTC under new drug applications generally involve ingredients that had a long marketing history as prescription products. The history of marketing in the prescription setting is important in providing safety information to support OTC marketing. When marketing under a new drug application, the same regulations for reporting

requirements that apply to prescription products also apply to OTC drug 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. Data on safety and efficacy was collected through public notice and comment for ingredients and their conditions of use.

The data was reviewed by an independent drug review panel and a panel report was published in the Federal Register. In the report, the panel makes specific recommendations on the efficacy and safety of ingredients for a particular category of product.

A comment period followed the publication of the report.

The FDA takes the report and public

comments to the report to develop a tentative final monograph, also known as a proposed rule. This proposed rule is published in the Federal Register for public comment. The comments are reviewed by FDA and a final monograph is written and published.

After the final monograph is published and the effective date 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 in the monograph.

Why now? The monograph for internal analgesic antipyretic and anti-inflammatory drug products is in the proposed rule stage. The proposed rule was published in 1988. The agency is attempting to finalize this rulemaking as part of the ongoing review, and as part of that review, we are looking at the most recent information available for several safety issues related to the ingredients in this monograph.

The category of products to be discussed today and tomorrow account for one of the largest segments of products used by consumers in the over-the-counter drug market in the United States. I suspect that the majority of folks in this room today have at least one of these products in their home

right now.

Ingredients marketed under the monograph include acetaminophen, aspirin, non-aspirin salicylates, and adjuvants, such as caffeine. Ingredients marketed under new drug applications include ibuprofen, ketoprofen, naproxen sodium, and acetaminophen for extended released products and suppositories.

I would like to make some important points regarding this category of 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. 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 OTC drug products is not an issue. The agency believes that these products remain available as over-the-counter drug products.

The subject for discussion today is unintentional acetaminophen overdose leading to hepatotoxicity. In February of 2001, the FDA and the Pharmaceutical Research and Manufacturers Association jointly sponsored a workshop to discuss drug induced liver toxicity.

During that workshop, Dr. Will Lee presented information on acute liver failure using a registry of patients on liver transplant lists. He found that 60 percent of acetaminophen related cases were due to unintentional overdose.

Dr. Lee will be presenting some of his data this morning.

I would just like to note that the FDA does not have access to Dr. Lee's data and, consequently, has not validated it. We do, however, believe that the data is important and should be part of today's discussion.

Dr. Lee's data prompted FDA to conduct a review of cases of hepatotoxicity reported with acetaminophen in the FDA adverse event reports database. Understanding that there are limitations in assessing causality with this database, there are cases that may be characterized as unintentional overdose, for example, when a consumer uses more than one product containing acetaminophen.

There are also cases of unintentional overdose reported in the literature. Acetaminophen hepatotoxicity can occur with the ingestion of a single large dose of acetaminophen as a means of committing suicide or with an accidental ingestion by

a child who gains access to a bottle of acetaminophen.

There are many products available over the counter, not just drug products, that can be used as a means to commit suicide. The issues related to the prevention of suicide are complex and extend outside of the discussion of acetaminophen.

For accidental ingestion by children there are already requirements for childproof packaging. Failures of childproof packaging is applicable to any OTC product and not just acetaminophen.

Consequently these nontherapeutic ingestions are not part of the discussion today.

The actual number of cases of unintentional overdose per year will be difficult to ascertain for a variety of reasons. Whether it is 25 cases, 50 cases or more is not the issue. The issue is can reasonable measures be implemented to prevent these events.

Even if there were only 25 cases per year leading to serious injury or death, if they are preventable with reasonable interventions, we have an obligation to attempt to reduce the risk of occurrence.

As part of your deliberations today, the committee will consider the following issues:

Are there identifiable circumstances or factors that contribute to these events?

Do we understand consumer or health provider behaviors that may influence the circumstances or factors?

Can the circumstances or factors be influenced by interventions?

Are there interventions that may prevent events or decrease the severity of events, or is additional research needed to address some of these issues?

That concludes my introductory comments. I would like now to introduce Dr. Bill Gilbertson from the Division of Over-the-counter Drug Products.

DR. GILBERTSON: I'm going to get to it. Left click. I'm not doing too well.

My opening remarks are going to be that I'm going to be very brief.

(Laughter.)

DR. GILBERTSON: There we go. Thank you.

Again, my comments will be very brief this morning. Actually I'm going to be talking about, specifically about the acetaminophen warnings that are limited in the rulemaking to the liver and to when it's used with alcohol.

Now, my task was to go back through the 25 years of rulemaking of the ingredient and to pick out those sections of the Federal Register that are most relevant to today's discussion.

What I did was I selected them out, and then I simplified them for purposes of this presentation. So here we go.

Back in 1977, the internal analgesic report was published and the advisory panel concluded that acetaminophen was safe and effective for OTC use at the doses described here, and in that report, it is stated that this ingredient is relatively free of adverse effects in most age groups, even in the presence of a variety of disease states.

Now, this action allowed this ingredient to be included into the monograph system. At that time, acetaminophen was marketed under a new drug application.

It was first approved in 1960, and it now had 17 years of marketing experience OTC. And it's important to note as I speak that the panel data and information was from the 1960s and early 1970s.

Now, the report included studies of patients with various forms of liver disease, and they found that several types of liver disease may prolong

the half-life of the drug, but they could not conclude that this increase would also increase the risk of hepatotoxicity, and they were unable to conclude whether it was safe for use in patients with preexisting liver disease. And they recommended that studies be performed to resolve this issue.

Now, there is a discussion in the report of cases of acute overdose with doses above 15 grams. They concluded that single doses of less than 15 grams are not usually associated with serious liver disease.

Now, there was a recognition that severe liver damage can occur if acetaminophen is used above the recommended dose, that is, four grams daily. And the panel recommended a warning, this warning: "do not exceed recommended dosage because severe liver damage may occur."

Now, following publication in the Federal Register, the agency received numerous comments obviously on this label. Some were opposed to the warning that made any reference to an organ or to be organ specific because it places the responsibility of recognizing organ damage on the consumer. It may be misunderstood or may alarm. It may encourage suicidal persons to abuse the drug. And it's inappropriate for

children's products because there is a lack of documented fatalities in children from acute overdose.

Incidentally, that comment did not provide any data to support that contention.

There were also comments in favor of a liver warning, arguing that there are no unique signs of toxicity like we have with aspirin, such as ringing in the ears, and that the symptoms of toxicity to acetaminophen do not appear until a few days after overdose.

And there is increased use of the drug. Fatalities and liver damage have occurred in children, and this warning may discourage consumers from exceeding the recommended daily dose.

In 1988, the agency published the tentative final monograph and broadened the adult dosage schedule providing for this 500 milligram dose. So we have a 500 milligram every three hours or 1,000 milligrams every six hours in addition to what was there before, but they still limited the maximum daily dose to four grams.

Now, the agency concluded that the data were insufficient to support the panel's recommended warning. The warning need to specify toxic effects to particular organs of the body caused by acute

overdose, and at that time we had no labeling in any products that I'm aware of that made specific reference like that to an organ.

However, liver damage can occur from overdosage and a warning statement is warranted. These are actual statements out of the Federal Register.

Now, the warning should emphasize the need for prompt medical attention since following overdosage there is a 24 to 48 hour period of relative well-being when symptoms of hepatotoxicity do not appear, despite the occurrence of liver damage.

So the agency recommended this warning. Actually the agency proposed the warning statement to immediately follow the required warning that's there now for "keep out of reach of children," and I've just highlighted that to show you where it would be placed in labeling. Prompt medical attention is critical for adults, as well as for children, even if you do not notice any signs or symptoms.

Now, even though an alcohol warning had not been proposed in the tentative final, many comments were received in favor of also including such a warning. Human and animal studies were cited contending that alcohol abusers us the drug within the

labeled dose.

And one comment even proposed that we label for alcoholic abusers a dose of a maximum two grams daily. Now, these comments are on public display in the Dockets Management Branch here in the Parklawn Building, and as a result, additional comments were received or I would call them reply comments opposed to such a warning, and these comments argued that the data were not rational; that the majority of the reports involved subjects with a history of alcohol abuse and use far in excess of the maximum daily dose; and that other studies were cited that disagreed with the animal human data that had been in the previous comments.

Now, in June of 1993, the agency presented this issue to this committee, this joint committee actually, in June of 1993. And the reason why I say June is because tomorrow I'll be talking about another meeting they had in September of that year for the salicylates and the NSAIDs.

The data that was reviewed by the committee were the issues that were in the tentative final that I've just discussed. The published reports of acetaminophen induced liver toxicity in alcohol abusers at various doses, phrarmacokinetic data on

acetaminophen metabolism in alcohol abusers, microsomal enzyme induction studies in subjects with liver disease, effects of alcohol abuse on acetaminophen overdose, and some animal data on the effects of ethanol in diet on metabolism and on glutathione levels.

The questions asked of this committee were: does the data support a warning for alcohol abusers?

What populations are at risk? Those that drink rarely, socially, and so forth?

And they asked such benefit-risk questions as: will alcohol abusers switch to other ingredients that have equivalent or greater risk?

What information should be included? Should we make specific reference to the liver and so forth?

And are the data sufficient to support a reduced maximum daily dose, two grams, for alcohol abusers? And if so, what should it be?

This committee concluded in June of 1993 that a warning was justified and should refer to possible liver damage. However, there was concern by this committee that the warning could cause alcohol abusers to switch to other products with equivalent or

greater risks and that it should not be implemented until the committee had an opportunity to look at the other analgesic ingredients.

And they also found that there was insufficient data to support a reduced maximum daily dose for alcohol abusers.

So the FDA concluded in 1997 that chronic heavy alcohol use or abuse has a significant effect on the metabolism and etoxification of the metabolite NAPQI; that alcohol abusers are at increased risk and a warning is warranted for adult products.

Organ specific warnings are more effective than general warnings, and we agree that there is insufficient data to support that lower dose, and labeling should recommend contact with a physician.

Now, these conclusions were included in a 1997 proposed rule. Comments were received, and they were pretty well equally divided in favor for and against the particular terms in that rule.

However, in 1998, the FDA published a final rule, alcohol warning. If you consume three or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain reliever/fever reducers. Acetaminophen may cause liver damage.

Now, all OTC acetaminophen containing products are required now to include this warning whether marketed under the monograph system or under a new drug application. So today we have this final rule in place, and we also have the yet to be finalized 1988 tentative final proposed warning about seeking prompt medical attention.

Thank you.

CHAIRMAN CANTILENA: Okay. Thank you, Dr. Gilbertson.

Now we have Dr. Senior also from the FDA, who will start the section of the program by the FDA that's scheduled for one hour.

Dr. Senior.

DR. SENIOR: Good morning. I'm John Senior, a hepatologist at the agency.

We are going to have a series of presentations from the Office of Drug Safety. Some of us will refer to acetaminophen. Some will use the abbreviation APAP. That's acetyl-para-amino-phenol, APAP. So both of these mean the same thing.

For eons of time, since pre-history, our ancestors have been making infusion of willow bark teas to relieve aches and pains. The active compound in that was identified in the early 1800s as

salycilin.

And then the German chemists in the late part of that century developed a series of compounds, including salicylic acids, some of which is still used as salicylates, and the common acetylsalicylic acid, which acquired the name aspirin just at the turn of the century.

At the same time, there were a number of other compounds that were found to be effective in reducing fever and pain, including acetanilide and phenacetin, which were used for a while, but turned out to be too toxic.

And it was found by Brody at the NIH in 1948-49 that both of these compounds were metabolized to a nontoxic compound that was N-acetyl para-aminophenol, acetaminophen, paracetamol in Britain, and APAP, the abbreviation.

However, it took a while before it became widely used. Aspirin was considered a wonder drug for the first half of the past century, but was found to cause a number of problems that you'll be discussing tomorrow.

Acetaminophen was approved shortly after Brody's work at the NIH was approved by the FDA in 1950, and then it was allowed to go over the counter

for consumer self-prescription and use in 1959.

Bear in mind that was before the amendment to the law that required the FDA to have proof of efficacy for drug products.

So acetaminophen came in as a nontoxic alternative to what was available, but in the British Medical Journal in 1966 Davidson and Easthan reported from Edinburgh two cases of fatal overdoses of acetaminophen in psychiatric patients.

Interesting and ironically, one had learned about the other one and went ahead and copied.

There was also another paper by Thompson and Prescott, another death from liver damage, another big paracetanol or acetamin overdosage and an editorial.

Now, the way this happens in the patients is insidious. The acute ingestion may produce some immediate nausea and vomiting and discomfort, but it all subsides and goes away for a day, two, three, and then on comes the bad stuff, the nausea, anorexia, vomiting, big, tender swollen liver.

The serum transaminases may go into the thousands, tens of thousands. The prothrombin time is elevated, liver failure, encephalopathy. The whole deterioration process ensues, as Dr. Lee will tell

you shortly.

Now, acetaminophen, the compound that was identified as this nontoxic derivative of the coal-tar compounds, is cleared out pretty quickly by glucuronidation on this phenolic group or by sulfation. The glucuronides and sulfates are made by really a -- catalyzed by a series, families of enzymes. There's a whole family now of these glucuronal transferases, and it has been recently stated that the glucuronal transferase isoform 1A9 is the one that particularly glucuronidizes acetaminophen.

Now, there was, in Brody's lab again, a number of really brilliant studies that were done and published in a series of four papers in 1973 that really opened up the understanding of what was going on in the toxicity.

Gary Mitchell and his colleagues working in Brody's lab described what was going on, and what they found in mice and rats, that the damage was related to the metabolism, not to the plasma level; that the damage was caused by covalent bonding of some metabolite, not the original compound, but something that was produced; then the enzymes in the liver called Cytochrome P450s catalyzed this reaction to

form this injurious metabolite.

And the glutathione depletion worsened it, and glutathione addition prevented the damage. That was pivotal because it suggested treatment.

Now, here's the metabolite that was found. The original compound, acetaminophen, is oxidized by this Cytochrome 3E1, the principal one, with minor contributions by some other cytochromes, to this oxidized, reactive intermediate called N-acetyl-benzoquinonamine, and we abbreviate it NAPQI.

This position or these other position equivalent is very reactive, very electrophyllic and wants to grab onto something. It loves to grab onto sulfur groups.

And there is another family of enzymes called glutathione transferases that catalyze the transfer of glutathione onto that group, again rendering it harmless for excretion.

If, however, all of those previous steps don't occur, this reactive intermediate may attach to cell proteins, to membrane proteins and cause cell death as a result.

Now, here's glutathione. This is as protective compound, and that sulfur group will attach here. It was suggested by the Brody and Mitchell

studies that you could use other substances and now we are using this drug, which we call Mucomyst in the trade name, but it's N-acetylcysteine, and that will attach also and protect from the deleterious consequences of the oxidized metabolite.

So we have inherently four lines of defense against overdoses or over amounts of this compound, as we have against many other things. A small amount is excreted unchanged, as unchanged drug.

Glucuronide conjugation is the principal way of getting rid of it. Fifty-five, 60 percent on average.

Conjugation with sulfate is another third or so, and then what's oxidized may be mocked up by glutathione and gets rid of most of the rest of it. So there's very, very little of the reactive intermediate left.

And if there still is some, you can still protect the patients with treatment, with Mucomyst, N-acetylcysteine, if you get there in time.

Now, when we have moderate chronic overdose as occurs in the unintentional patients, we don't know the moment they took the overdose. In this country, somewhere between a third and a half of the patients may be unintentional. The rest may be

depressed, suicidal patients.

In Britain, this number is even lower.

However, they may have none of those prodromal symptoms, and a question remains as to whether doses somewhat over the recommended dose may be dangerous if the enzyme systems are induced.

Data are really not sufficient yet to conclude on this.

On the other hand, people who take acetaminophen chronically may become tolerant, and Martin Black, a friend and colleague in Philadelphia who had worked with Mitchell and Brody at NIH, had a patient come to him who was taking as much as 65 grams of acetaminophen a day without liver injury, without significant liver injury.

He was addicted to percodan, and he was taking the combination percodan and acetaminophen together.

The plasma levels may not always be helpful in these unintentional cases because you don't know when they took the overdose or whether it was accumulation, and it may be too late for effective treatment.

So there are a zillion factors affecting the absorption and metabolism. The National Medical

Library PUBMED system discloses literally hundreds of papers on these subjects. There's variation and dissolution, gastric emptying, all the rest of it. Every one of these steps is highly variable, and some of the factors are known.

There are also a lot of drugs, a lot of compounds that induce the enzyme systems. The liver has to handle simultaneously not only drugs, over-the-counter remedies such as acetaminophen, alcohol, dietary supplements, compounds from the environment, internal compounds, all at once, and they all interact with each other and affect the metabolism

So we have then at the end of the day a huge problem of enormous variability in the amount of the toxic compound that we worry about that injures the cells and kills the patients.

The paper by Kritchley (phonetic) and Prescott, Prescott has really made a life study of the metabolism and pharmacology of acetaminophen. A 60-fold variation from one person to another. Now, that cannot be dealt with by taking the average for the group.

It is very clear that the average dose for the average person is safe, but we are not all average people, and a dose that is safe for most people may

not be safe to some people. And consequently, larger doses that are not tolerated by most people may be tolerated if you develop -- you have become tolerant to long ingestion.

So there are many, many interactions, and we're just beginning to learn about many of these things. This is really an update of the previous work that was just summarized recently.

So I offer these considerations for you to think about as you hear the arguments pro and con about the studies that have been reported. Bear in mind the physicians are concerned about individual patients who are really statistical outliers. They are not concerned about the median number, the average person in a group that is normal and not affected.

So we have to bear those in mind as we consider these issues further.

Thank you.

CHAIRMAN CANTILENA: Thank you, Dr. Senior.

Dr. Lee, please.

DR. LEE: Thank you, John.

My brief here is to talk about the acute liver failure study group and specifically about cases of acetaminophen which I've termed in the past

accidental, and maybe I need to change it over to unintentional, but if you see the word accidental, we don't mean children taking overdoses accidentally, but rather the so-called unintentional cases.

Now, this is the picture at autopsy of a liver, of actually a halothane case, but it just introduces the topic of acute liver failure. What we're talking about here is a severe hepatotoxic injury to virtually all of the hepatocytes as seen in this low power photomicrograph.

The clinical features that are characteristic of it and mark the severity of the injury are highlighted by the alteration in mentation. No patients in the acute liver failure study group that I'm going to show you were admitted to the study without having this cardinal feature and without having some degree of coagulopathy.

Now, again, we're not talking about patients with chronic liver disease, with cirrhosis. They have to have had an acute illness, and varying definitions have been used: less than eight weeks, less than 26 weeks.

But in most instances the acetaminophen insult is less than a week in duration, with previously normal presumed at least hepatic function.

The interesting thing about acute liver failure is that you have a common clinical syndrome which applies to virtually all cases, and the feature, again, are the altermentation, but also in many, if not most of them, some degree of brain swelling or cerebral edema.

The background for this is that its actually fortunately a very rare disease. There are probably somewhere around 1,000 to 2,000 cases per year. This is a guesstimate, not based on our data, but from previous NIH consensus conferences related to this.

And as a result, we formed the acute liver failure study group on the premise that most series prior to our coming on line in 1998, most series were single center reports over ten or 14 years, as I'll show you in a moment, and certainly most centers, even a major transplant center, will only see a handful of cases of acute liver failure each year.

Similarly, there's no viable treatment for all patients. We deliver pregnant women who have acute liver failure. There is an antidote for mushroom poisoning, and there's certainly use of N-acetylcysteine for acetaminophen poisoning, but other than that, there's no treatment.

So we were looking to develop a consortium to do a treatment trial for perhaps the non-acetaminophen cases, and I'll talk about that momentarily.

The early trials or the early registries or series that were published had mortality rates over 90 percent even in these small, single center studies. We now, since about 1981, do transplantation. These are the patients that have the highest listing in the UNOS transplant list, but the question is how often do they get transplanted and how effective is it.

So this is a group that I began setting up in 1996 and 1997 initially with 14 academic medical centers, all of whom preform transplants except one, and we began collecting prospective data in 1998.

We now have 25 centers, and since the year 2000 began, a pediatric collaborative study of similar fashion employing 23 sites around the U.S.

We have two or three missions. One is to collect detailed prospective data and serum samples on cases meeting the criteria that I outlined before.

We are also doing an N-acetylcysteine trial for non-acetaminophen cases, not the topic today, and we do numerous ancillary studies relating to etiology of the indeterminate group and various

other aspects.

We have been funded initially by NIDDK with an RO3 grant; then subsequently for the NAC trial by the FDA Orphan Products Program, and we now have an NIH RO1 grant, which we are now starting the third year thereof.

We collect data once informed consent is obtained from next of kin since the patient is always mentally altered. We collect prospective data on five page case report forms shown here on admission, and then a subsequent case report form at the outcome, that is, hospital discharge, transplant or death.

We are doing long-term follow-ups, but that's just in process now. But anyhow, when I talk about outcomes, such as transplantation and death, we'll be talking about relatively short-term outcomes.

Now, just to backtrack for a moment, I mentioned some of the earlier studies prior to our own. Here's a listing of five different studies prior to 1998, and you notice that this study, which was U.T. Southwestern in really the pre-transplant ear, had no acetaminophen cases, mostly Hepatitis A and B, although they weren't called that at the time. It was infectious and serum.

In Rakela's study, which was a multi-

center study, again, in the '70s, no acetaminophen cases. In Rakela's later Mayo Clinic study, again, over approximately nine years non acetaminophen cases.

And then the first appearance of acetaminophen cases in a registry is the study of Shakil from the University of Pittsburgh, at that time the biggest transplant center in the U.S.

And, again, note that this is over a 12-year period, and the total n of all cases was 177. But in any event, 20 percent or 19 percent of the cases were thought to be due to acetaminophen toxicity.

Now, again, we haven't specified accidental or suicidal in that study.

This was a retrospective study that my group did in trying to get funding, frankly, for that first RO3 study. So I asked the 14 sites that were invited to participate to collect two years of their transplant database registry regarding several things, just very basic data: age, gender, presumed etiology, and outcome, and coma grade on admission.

And in that study there was 20 percent acetaminophen toxicity listed as the primary cause by the site investigator.

Now, this is the overall data from the

prospective study, the going forward study from 1998. Currently we are over 450 cases, but this is a snapshot when we were at 395 cases, and you see that -- and these are the numbers here -- that in the current study roughly 40 percent or 160 out of 395 appear to be related to acetaminophen toxicity.

By comparison, 49, or something like 12 percent, are related to all other idiosyncratic drugs; Hepatitis B down to about eight percent; Hepatitis B, something like four or five percent, and so forth; with a still indeterminate group of somewhere around 18 percent.

Again, the snapshots have been take at various times. The largest series that we've examined intensively has a smaller n of 308, and I'll show most of the data that you'll see, such as this slide here, reflects the n of 308, which was just slightly earlier in our data collection.

Now, this slide shows the retrospective study in orange that I mentioned a moment ago, the 1994-96 transplant registry study compared to our prospective study in the light blue here. And you see there are some differences.

In gender the earlier study appeared to have only 54 percent women, whereas the current study

has something around 73 percent female preponderance.

In the earlier study there was 20 percent acetaminophen. In the current prospective study, there's 40 percent, and so forth.

There are minor differences here. There's few numbers transplanted overall in the prospective study, and greater spontaneous survivors.

The differences here, we believe, are due to the differences in data collection. That is that if you simply collect from a transplant database, you may exclude a lot of the acetaminophen cases. So to collect all of the cases that have acute liver failure, including ones that may not be considered for transplant or listed for transplant, you will have a larger number of cases, and a number of the acetaminophen cases will fall into that group.

There are a number of reasons why acetaminophen patients don't get listed for transplantation. One is their general good outcome, but another is the psychosocial milieu surrounding each case.

Now, this is a busy slide, but if you concentrate just on the two left-hand columns, you see what the clinical picture is for a group of 120 cases. This is, again, out of the overall n of 308. Again,

for the acetaminophen cases, a high preponderance of women, but note that there are more women in the idiosyncratic drugs and basically in all of the categories of acute liver failure, and we don't understand that, why that should be.

Notice the differences in these cases. The length of illness is very short. One day of jaundice preceding onset of encephalopathy versus typically in the idiosyncratic drugs 12 days. The degree of coma, the severity of the disease, if you will, on hospital entry is equivalent between all ranges, but note the very high aminotransferases, which Dr. Senior alluded to earlier versus lower aminotransferases in the idiosyncratic group.

But notice also with a very short duration of illness, low bilirubin here, much higher bilirubin again indicating a much longer disease duration.

Notice also the differences in the percent transplanted. Only six percent of the acetaminophen cases got transplanted, 6.8 percent spontaneous survival, for an overall survival of 73 percent. Still a quarter of the patients with this condition do die.

By contrast, more than half of the idiosyncratic drug cases need to be transplanted, and

very low spontaneous survival, and this, again, reflects the overall picture prior to the transplant era when most patients with this condition went on to die.

Now, just to digress for one second, around the world there's quite a difference in the cases. Dr. Senior alluded to the United Kingdom where in one study from King's College Hospital in the '90s there was 73 percent acetaminophen or, as they say it, paracetamol overdoses.

And, again, these they claim are virtually entirely suicidal overdoses.

Now, again, I've used the term "accidental," and I'll correct it to "unintentional" versus "suicidal." When we talk about the cases that I'm going to now show you two or three slides on, the suicidal cases we define as having a history of a single time point ingestion -- I think that's key -- with suicidal intent, whereas the unintentional cases are multiple time point ingestions, typically have a cause for pain identified, and deny suicidal intent.

Now, let me digress one more moment and remind you that this is, again, not the total universe of patients that get admitted to the hospital with acetaminophen hepatotoxicity. We outlined this, and

others have, Madre and Sief and Zimmerman, through the '80s, and we did this study of a 40 month examination of all the cases coming into Parkland Hospital that had this as their main diagnosis.

And we came up with, as it shows here, a total of 71 cases admitted over 40 months with accidental or suicidal ingestions leading to potential or accomplished hepatotoxicity. Now, again, this is not all getting to acute liver failure. Only a small fraction of them would have reached that endpoint.

But clinically these cases are very different in that the accidental cases typically present late, after 24 hours, whereas virtually all of these suicidal cases are in the emergency room within four hours of the ingestion. They announced that they've taken an overdose, and they're brought in, and they get N-acetylcysteine quite early.

In that study, we saw a lot of alcohol abuse, particularly in the accidental or unintentional group. Again, because they come in late, they have low acetaminophen levels versus the early presenting suicidal cases.

The late presenting cases tended to have higher aminotransferase levels, again, when you consider all people entering, because as it shows

here, only one in five of the suicidal cases ever got an aminotransferase level greater than 1,000. This should be greater than.

Most patients in all categories receive N-acetylcysteine or at least at Parkland Hospital they do, but the outcomes are worse for these so-called accidental cases.

So more of the accidental cases on a percentage basis at least get to the threshold of acute liver failure.

Now, back to the current data. When we had the 120 cases, to analyze this cohort separately, we actually deleted at 12 because in each of the 12 there might have been a concomitant issue, Herpes Simplex infection, possible idiosyncratic drug reaction, and so forth.

So the 108 cases was our analysis of ones that appeared to be purely related to acetaminophen hepatotoxicity. Once again, you've seen some of the numbers, 79 percent women. Alcohol use was 57 percent. Again, alcohol abuse in this group was only 19 percent.

What's new to us at least was that nearly 40 percent were ingesting narcotic combinations, that is, vicodan, percocet, and so forth, largely vicodan,

by the way, and that these people were ingesting these drugs for as long as two or three months, typically in doses above those on the package labels.

And, again, somehow the computer has changed these symbols. It's Mac versus PC here. This should be dose greater than four grams per day, 69 percent; dose greater than ten grams per day, 32 percent. Again, acetaminophen level detectable on admission, 82 percent, greater than 50 milligram per liter acetaminophen level would be 42 percent.

Aminotransferase greater than 7,000 international units more than half of the cases, and greater than 3,500 92 percent of the cases, and again, this is creatinine greater than two, 52 percent; and pH less than 7.3, 17 percent. So not very many of the cases become acidotic.

Now, again, we use this same criteria for dividing the so-called accidental from the suicidal cases. This does not add up to 108 because there were five cases where we could not determine intent. If you examine the suicidal and the accident cases, they actually look quite similar in terms of the dosing; a little bit different in age in the accidental cases being older.

Interestingly they both have roughly the

same degree of antidepressant use reported, roughly the same degree of alcohol use. This, again, is not abuse but use.

A use of more than one acetaminophen compound at the same time was quite common in the unintentional overdoses. Again, the narcotic acetaminophen use was more common in the unintentional overdoses.

The aminotransferase levels on the whole in this study, again, remember this is different from the Parkland study. This is only people who reach the threshold of hepatic coma, some degree. The aminotransferase level was low, suggesting it's a little bit more subacute than these cases. The creatinine was higher, and the overall survival is similar.

So I think once you reach the threshold of acute liver failure, the cases, whether they're unintentional or intentional, are quite similar in their characteristics.

What's the outcome? Basically for the overall study, again, the 308 patients I described, 43 percent survived without transplant. Only 29 percent get transplanted, and this has partly to do with the organ shortage in the U.S., and only 84 percent of

them have short-term survival.

Twenty-eight percent die before transplantation, some of them being listed, some of them not being listed, and still the most common cause of death in those who died without a graft was acetaminophen hepatotoxicity, representing about ten percent of the overall group and about 25 percent, again, of the acetaminophen group.

So in summary, acetaminophen still accounts for about a third of all the deaths in this series. It seems to be the most common cause by far, and possibly growing in the U.S. This estimate is just a ballpark estimate of the number of cases, not number of deaths. It's very hard to get this data.

In our most recent studies, the relationship to alcohol abuse may be present in some cases, but it's a relatively small number. Clinically the accidental and suicidal cases look similar to each other once they reach the threshold of encephalopathy.

And we still have relatively low mortality in these cases, but many of them are not listed for transplant.

What I think is interesting perhaps is the role of antidepressants, the role of narcotics particularly as John alluded to, the build-up of

dosing of six to 12 grams per day of narcotic plus acetaminophen, and in these cases, we honestly don't know what's going on.

If they could tolerate, let's say, six or eight grams per day of acetaminophen, then why did they get sick on the day or two that they came in?

Again, repeated daily dosing and use of multiple preparations is a problem in a small fraction of cases, and in our pediatric series, about 20 percent of these cases are apparently acetaminophen related.

Thank you very much.

CHAIRMAN CANTILENA: Thank you, Dr. Lee.

Our next three speakers are also from FDA, Dr. Nourjah, Dr. Ahmad, and Dr. Karwoski.

DR. NOURJAH: Good morning. My name is Parivash Nourjah, and I'm from Office of Drug Safety.

I'm the first of three speakers today who will talk about the safety analysis of acetaminophen associated hepatotoxicity.

This is an overview of our presentations. I will present the national estimates of acetaminophen associated overdose. Dr. Ahmad will follow with a review of the literature and poison control data. And Dr. Karwoski will conclude with a

summary of FDA spontaneous reports of APAP associated hepatotoxicity.

APAP associated hepatotoxicity has been reported with intentional overdose, unintentional overdose, or rarely as recommended doses.

The objective of my talk is to present the estimated number of overdoses associated with APAP, particularly related to unintentional overdoses.

Source of data. For my analysis I used four national databases. First, the national hospital ambulatory care survey, the emergency department component of this survey.

This is a probability survey sampling of visits made to emergency department of non-federal, general, and short stay hospitals in the U.S.

Second, the national electronic injury surveillance system, all injury program. This survey collects information on concealment product related injuries treated in emergency departments of 60 selected hospitals.

Third, the national hospital discharge survey. This is a probability survey sampling of in-patients' discharges from non-federal, short stay hospitals in the U.S.

And fourth, multiple cause of death files,

a data file that contains information from death certificates.

These four files provide national estimates.

This slide summarizes my findings from analyzing the mentioned databases. These groupings are independent of each other and represent annual averages in the U.S.

Let me remind you that these numbers represent overdoses without any mention of hepatotoxicity. Annually there were over 56,000 emergency department visits, more than 26,000 hospitalizations, and 458 deaths associated with APAP.

These numbers represent both intentional and unintentional overdoses. The definition for intentionality that are used for our analysis depend on the data source. For the hospital discharge and mortality data, I used ICD-9 code. APOP overdoses were classified as intentional cases when they were codes for suicides or overdoses due to other substances, while unintentional cases were defined as those with a code for accidental overdoses by APAP, and there was no indication of suicide, overdose to other substances, or depressive disorder.

For the emergency department data, I

review comments field and classify intentional cases as those with mentions of suicide or suicide ideation, and unintentional cases as those with mentions of accidental ingestion or therapeutic misuse.

Children less than six classified as accidental ingestion unless it is stated otherwise.

This slide represents the number of estimated cases of unintentional overdoses. Again, these groupings are independent from each other and represent annual averages.

There were over 13,000 emergency department visits, more than 2,000 hospitalization, and 100 deaths associated with APAP.

I attempted to examine possible risk factors associated with unintentional overdoses. My analysis was limited because certain variables were under reported or simply not reported at all.

Additionally, the sample size was too small for exploring certain variables.

I was interested in exploring the age distribution for APAP overdoses since it is known that the medication utilization varies by age and different APAPs are available for different ages. I examined the age distribution for cases in three databases to see if there were differences for the age groups. I

find that the age distribution varies by settings.

Young people were the highest percentage of cases in the emergency department and accounted for 23 percent of hospitalized cases and less than two percent of deaths.

Chronic liver disease has been postulated to be one of the factors that increases the risk of hepatotoxicity from APAP. Using the multiple cause of death database, I examined the presence of non-IQ liver disease among those with unintentional and intentional overdoses. I found that among the unintentional cases, 13 percent have chronic alcohol liver disease, and 42 percent had some other chronic liver disease.

This finding suggests that chronic liver disease may be a risk factor for developing or increasing severity of hepatotoxicity among patients experiencing unintentional overdose.

This analysis may be limited because the diagnostic information may be misclassified. First, if alcohol is not mentioned on the death certificate, alcohol related liver disease may be misclassified as other chronic liver disease.

Also, some diseases may be acute, but identify as chronic.

Second, suicidal cases may be misclassified as unintentional overdose to protect the patient's family from a stigma.

There may also be detection bias because the contributing cause of death may be investigated more with unintentional APAP overdoses than when the cause of death is known to be suicide. Thus, liver diseases may be reported more often.

Finally, and potentially most importantly, death certificate information, such as the circumstances that led to death, for example, whether it was an accidental overdose or the body system injured, such an acute liver injury may not be consistently reported, and thus there may be underestimated of these variables.

In conclusion, in this review of the number of cases of APAP associated overdoses, I found that children account for at least 22 percent of the hospitalized cases of unintentional overdoses.

Additionally, the observed association of chronic liver disease with unintentional APAP overdoses suggests that preexisting liver disease, both in the presence and absence of alcohol, may increase the risk of severity of APAP associated overdoses.

This is the end of my talk, and I introduce Dr. Ahmad.

DR. AHMAD: Good morning. The objectives of my presentation this morning are to identify case trees (phonetic) of APAP associated hepatotoxicity in published literature and to study the extent of APAP associated fatalities reported to poison control database.

A MEDLINE search was done to identify APAP associated hepatotoxicity literature. The review was restricted to USK series, which at least ten cases published in the U.S. literature in the last ten years. Eight publications were identified and four of which cases were collected exclusively of review of hospital medical charts and two case series, cases that were obtained from hospital medical charts plus published cases.

And in one case series from a registry of cases contributed by hepatologists and other practitioners, and one exclusively from a consortium of liver transplant centers.

The number of cases per series ranged from 47 to 73. Two were pediatric case series and the remaining six slightly adult case series.

Gender was reported in six case series,

and there was a preponderance of females.

Of the eight case series intentionality was mentioned in five. This slide gives the dose range in these five studies. In three of these studies, there were cases where APAP was ingested at recommended dose, that is, four grams per day or less.

In the Johnson case series, there were nine, or 17 percent of cases, who ingested APAP at four grams per day or less. The mean dose ingested ranged from 1.3 to four grams per day. All of these nine cases had a history of alcohol use. The age range, from 27 to 58 years. There were six males and three females. Days of use ranged from one to seven days.

Now, let me say a few words about the one case which ingested a mean dose of 1.3 grams per day of APAP. This was a 47 year old male who ingested a mean dose of 1.3 grams per day for two days to treat alcohol withdrawal symptoms and died.

In the Schiodt case series, there were three of 14 person cases in the unintentional group who ingested four grams per day or less of APAP. All of these cases were possibly related to fasting and/or alcohol use.

In the Zimmerman case series there were 27

of 40 person cases who took APAP at recommended dose. In addition, there were 13 of 20 person cases who took APAP between 4.1 to six grams per day. All of these were regular alcohol users.

In the Whitcomb case study, there were three cases who ingested APAP at or slightly above the recommended dose. APAP dose was ingested between 3.5 to five grams per day in one case and four to six grams per day in two cases. One case had a history of recent fasting, and the other two had a history of both fasting and alcohol use.

In the Broughan case study, there were no cases that ingested APAP at recommended dose.

This slide compares these outcomes and deaths in the unintentional and intentional groups. These outcomes were defined as hepatic coma, acute liver failure, and liver transplant. You will notice that there were a high number of deaths and serious outcomes reported in the unintentional group.

In other words, in two case series where intentionality was noted more severe hepatotoxicity evidence by severe liver injury, higher transaminase levels, longer lengths of hospital stay, and more deaths were seen among unintentional cases compared to intentional group.

Now I would like to search case and describe data from Poison Control Centers. Tests or toxic exposure surveillance system is the poisoning database of American association of Poison Control Centers, and currently has a repository of over 27 million human poison exposures reported by over 60 participating Poison Control Centers covering over 90 percent of U.S. population.

We reviewed annual reports from 1995 to 1999 and included only cases that listed APAP as the primary first agent. APAP is the leading cause of poisoning in tests. In 1999, APAP related calls represented ten percent of all calls to Poison Control Centers.

There was a slight decrease in calls from 111,000 in 1995 to 108,000 in 1999. In 1999, nearly 50 percent of calls were treatment and health care facilities and two percent of calls had major effect, that is, the signs or symptoms occurring as a result of APAP exposure were life threatening or resulted in significant disability, and more than half the calls involved children and adolescents.

Of all APAP related calls in children under six years of age which represented about 40,000 calls, 22 percent of these occurred in children who

ingested adult formulations of APAP.

In 1995, overall APAP related fatalities were at least 76, and this increased dramatically to 141 in 1991. APAP is the leading pharmaceutical agent associated with deaths in tests and represented about 60 percent of all deaths that were reported to tests in 1999.

This slide gives a breakdown of the intentionality among 141 APAP related fatalities in 1999. Sixty-five percent of the cases were suicidal and 30 percent of the cases were unintentional.

We included therapeutic error, unintentional, unknown, intentional misuse, and adverse drug reaction in the unintentional group.

We included intentional misuse since these were not classified as suicides and assumed likely to represent individuals who ingested excessive APAP with therapeutic intent.

This slide describes the number and types of APAP formulations that were associated in unintentional fatalities. Sixty-five percent of deaths occurred in individuals who took single ingredient APAP product which are available over the counter. Nine percent deaths occurred in individuals who took prescription APAP product, and 26 percent

occurred in individuals who took multiple APAP products simultaneously, which included an OTC plus prescription, two prescription products, two prescriptions and an OTC, and two OTC products.

The current limitations of tests. Under reporting may be extensive. Serious cases may go directly to emergency department and may not be captured by poison control centers. Chronic users may not be captured by poison control centers.

In conclusion, there are a small number of published cases of APAP related toxicity at recommended dose, some of which occurred in the setting of alcohol use and of fasting. Unintentional cases are associated with more serious outcomes, including death, compared with intentional cases.

Use of adult formulations of APAP in children under six years of age accounted for 22 percent of APAP related calls.

And finally, among unintentional fatalities, 26 percent were due to use of more than one APAP product simultaneously.

Now, let me introduce you to Dr. Karwoski, who will summarize spontaneous reports of APAP associated hepatotoxicity seen in AERs.

Thank you.

DR. KARWOSKI: Good morning. My objective is to describe the circumstances that led to hepatotoxicity in individuals who ingested one or more APAP containing products.

The review was of spontaneous reports in the adverse event reporting system, and our focus was on cases without apparent suicidal intent.

Our criteria included U.S. cases received by the FDA between January 1998 to July of 2001. Cases reported at least one APAP containing product as suspect resulting in hepatotoxicity. Cases without apparent suicidal intent were included in our review.

Of 633 reports, 43 were duplicates and 283 were excluded for various reasons, primarily for suicidal ingestion.

We ultimately reviewed 307 cases of which 25 were pediatric and 282 were adults greater than 12 years of age. These will be summarized separately.

Among pediatric patients, the ages range from less than one day old to eight years. Males represented about 70 percent of the cases that reported gender information.

Fifteen of the 25 cases were categorized with severe life threatening liver injury. Of these, ten died. Twenty-one of the 25 children were

hospitalized, and two were seen in an emergency department.

The milligram per kilogram per day dose was estimated based on reported daily doses and weight, and ranged from 106 to 375 milligrams per kilogram per day. This information could only be estimated in ten cases.

The recommended pediatric dose is 75 milligrams per kilogram per day.

Most of the children were receiving only one OTC APAP containing product. Single ingredient or an unspecified APAP product was most commonly reported. Of the single ingredient products, the concentrated drops were reportedly used in seven cases.

Medication errors leading to overdose and hepatotoxicity was noted in 20 cases. In some cases, more than one error was possible. Errors related to product confusion include use of the wrong formulation, such as the use of the concentrated drops instead of the children's APAP formulation.

The concentrated drops are three times as concentrated as the children's APAP.

In four cases they described the use of an incorrect measuring device, such as using teaspoonfuls

instead of dropper fulls.

Five cases reported misinterpretation of dosing guidelines on the label or instruction provided by a health care provider. Use of more than one APAP containing product may have been a factor in three cases, and there were other cases that could not easily be categorized.

Factors leading to hepatotoxicity were unknown in five cases.

Additional possible contributing factors were noted in ten cases. Co-suspect medication use was reported in six, and possible underlying liver disease was reported in four cases.

Of the adult patients, the ages ranged from 15 to 85 years. Females represented just over 60 percent of the cases reviewed. One hundred sixty-nine cases were categorized with severe life threatening liver injury. Of these 124 died, and seven required liver transplant. Two hundred and twenty-nine patients were hospitalized.

We used the indication for use or diagnosis for use as a surrogate for intentionality. One hundred and ninety-nine cases, or 71 percent of the adult cases, reported using an APAP product for a therapeutic indication, primarily analgesia. In 74

cases, the indication for use was unknown, and nine cases reported abuse of an APAP product containing a narcotic.

One hundred and 38 cases listed an unspecified APAP product. It is unknown whether these were single ingredient or combination products that were either OTC or Rx. One hundred and twenty-two, or 33 percent of all cases, reported the use of an Rx combination product with a narcotic, and an OTC single ingredient product was listed in 76 cases.

Where the dosage strength was known, 500 milligrams was reported most often. Approximately 25 percent of all individuals took more than one APAP product, and if more than one product was reported, it more often included the use of an Rx product with a narcotic in combination with an OTC product.

The daily dose was estimated in 132 cases. If a dose range was provided, the midpoint was used, and if the strength was unknown, a 500 milligram dose was used.

Of all cases in which the dose was estimated, the mean and median dose was six and a half and five grams, respectively, but ranged from 650 milligrams to 30 grams per day. This was across all levels of severity of hepatotoxicity.

Sixty-five of the 132 had severe liver injury, and their mean and median dose was slightly higher, at 7.1 and six grams, respectively. Twenty-three of these reported using less than or equal to four grams per day, which is the recommended dose.

Individuals that use more than one APAP product also reported higher doses. In 43 cases, there was qualitative dosing information provided, wording such as excessive use or excessive doses. Of these, two thirds suggested that greater than recommended doses were used, and in 107 cases, there was no dosing information.

Alcohol use is not a standard field that is collected in the AER system. So conclusions about this variable must be made with caution since the information may vary with reporter.

Alcohol use was reported in 116 cases. These were broadly described as alcoholism or alcohol abuse in 64 cases, regular, daily, or moderate use in 23 cases, occasional use in ten cases, previous use in six, and 13 did not provide a description.

Eighty-six of the 116 alcohol users developed severe liver injury. For those that provided dose information, the mean dose was lower for users versus those that did not report alcohol use.

In the table, the first row shows the mean dose of patients with an alcohol history versus those with no history. This is among all cases that reported dosing information.

The second row shows these doses in patients that develop severe liver injury.

A history of liver disease or possible underlying liver disease was reported in 70 cases. At least 20 were reportedly due to alcohol. Twenty-three reported a history of possible viral hepatitis. Forty-nine of the 70 cases developed severe liver injury.

And, again, the mean and median dose for those patients with liver disease was lower compared to those that did not report liver disease.

The table that's similar to the previous slide with the first dose shows the mean dose of patients with liver disease versus those with no disease, and this is among all cases that reported dosing information.

And the second row, again, shows these doses in patients with severe liver disease.

Co-suspect medication use was reported in 93 cases. Sixty-three of these were labeled for hepatotoxicity. Information regarding fasting or

malnutrition is often not captured, but we did note a small number of cases that reported malnutrition or decreased PO intake.

I'm going to go back to the 23 cases of severe liver injury that reported doses of less than or equal to four grams. Among these 23 cases, 18 reported risk factors. Eleven reported more than one risk factor. Fifteen had a history of alcohol use. In ten they were described as alcoholism or alcohol abuse.

However, there were five that reported regular or occasional use. Thirteen reported liver problems, including alcoholic liver disease and four viral hepatitis in four case and five others reported other abnormalities. Three reported poor nutritional status.

The circumstances were unclear in five cases with no reported risk factors. Other possible contributors in two of the five cases were concomitant use of phenytoin and possible sepsis in two.

There are some limitations to the data I've presented today. Dosing information may be unreliable. APAP products are generally taken on an as needed basis, and so the actual dose ingested can be difficult to ascertain.

There is no certainty that all of the adult cases were unintentional. There may be a stigma associated with reporting suicide and, thus, cases may be reported as unintentional when they are actually intentional.

For all spontaneous reporting systems there is no certainty that the drug caused the event. We lack an accurate numerator and denominator. Therefore, incidence rates cannot be determined, and spontaneous reports are subject to under reporting with only one to ten percent of adverse events reported to the FDA. This may be more significant for OTC products.

In conclusion, our review of the AERs cases identified circumstances that likely let to hepatotoxicity. Errors related to product confusion were mostly observed in pediatric cases, and these errors primarily relate to confusion over varying product formulations and strengths and use of inappropriate measuring devices.

Many adults were taking too much APAP, and in some cases, use of multiple APAP containing products likely contributed to hepatotoxicity.

Risk factors such as alcohol use or liver disease were also identified and may lower an

individual's threshold for APAP hepatotoxicity.

Questions remain that were not answered by my analysis. Do user lack knowledge of the potential for hepatotoxicity when using an APAP containing product?

Do users lack knowledge of the symptoms of hepatotoxicity? A lack of knowledge may lead to a delay in medical treatment.

What is the role of malnutrition and fasting?

What is the contribution of concomitant hepatotoxic medication?

And finally, what additional factors place a small number of individuals at risk for severe hepatotoxicity at or slightly greater recommended doses?

The Office of Drug Safety Analyses from all three presentations have shown that unintentional APAP associated overdoses have been associated with a large number of emergency department and hospital admissions and an estimated 100 deaths each year. Unintentional APAP associated overdoses are preventable.

Using a number of data sources, our analyses have shown that circumstances leading to APAP

hepatotoxicity are multi-factorial. APAP is present in multiple prescription and OTC products.

Additionally, these products are available in numerous strengths.

Given the observation that a number of cases have occurred from multiple product use and overuse, there is likely to be a lack of knowledge about the safe use of APAP.

Our review of the multiple data sources presented today identify alcohol, underlying liver disease, and fasting as risk factors that may lower the potential for hepatotoxicity with APAP.

We believe that a variety of risk management and communication interventions should be considered to address unintentional APAP associated overdoses leading to hepatotoxicity.

Thank you.

CHAIRMAN CANTILENA: Okay. Thank you, speakers from the FDA.

We now have an opportunity to question the speakers from the FDA, and while you're getting ready with your questions, I would actually like to ask the first one to Dr. Lee, and actually it's really asking for a comment or even to get you to speculate for us why four fifths of the individuals are female, you

know, in your group.

DR. LEE: The question was why are so many of the cases that we see women. I don't think we have an idea whether it's more frequently turning to a pain reliever, and I think there is some NHANES data that suggest that women more commonly will use pain relievers than men overall in the U.S.

But you notice that there was a higher incidence of women in all the categories. So there may be some intrinsic difference in dosing or in metabolism in women. I honestly don't know.

CHAIRMAN CANTILENA: Okay, and then if I could just perhaps ask Dr. Watkins to comment on the issue of, you know, gender effects with the SIP enzymes.

DR. WATKINS: There are well recognized sex differences in drug metabolism in rodents, but consensus, I believe, is in man that differences are very small if they exist at all.

There are certain examples of enzymes where you can make a good argument that there are differences in metabolism, but in the enzymes that are relevant to acetaminophen metabolism, to my knowledge, there is no data suggesting sex differences, for instance, in Cytochrome P450-2E1, for instance.

Now, there are other people, such as Alastair Wood who have considerable experience in this area and might also have a comment.

DR. WOOD: No, I think that's right. Paul summarized it reasonably.

CHAIRMAN CANTILENA: Okay. Dr. Katz, do you have a question for Dr. Lee?

DR. KATZ: yes, thank you, and this could equally well go to any of the FDA folks.

I'm struggling with the issue of association versus causality and the acute liver failure data and in the other data as well, and obviously acetaminophen exposure is ubiquitous in our society. Exposure to combination opioid products containing acetaminophen is also ubiquitous in our society.

And I'm wondering how you dealt with the issue of association versus causation with acetaminophen and liver failure.

DR. LEE: Sure. I think this is a hard problem, and I should point out I didn't have a limitation slide, as most of the FDA speakers did, but you have to remember that these patients are all altered mentally when they enter our study.

Now, we're getting historical information.

It is a prospective study. So our investigators are usually on the scene, but there may be other information that could have been garnered from the referring hospital, and many of our cases are -- something like 82 percent are referred in from another hospital.

So the primary data, in part, is from family and part is from patient if they're still awake, and then part is from referring hospitals.

I would say we have three main criteria. One is history of an ingestion of more than four grams per day, and that was fulfilled by, I think, something like 92 percent of the cases.

Presence of an acetaminophen level clearly doesn't necessarily imply hepatotoxicity, but if there is hepatotoxicity and there is any acetaminophen in the system, that is certainly suggestive, and acetaminophen levels being absent doesn't exclude it, but something like 69 percent of our cases had an acetaminophen level, and 52 percent had I think it was -- had greater than 50 grams.

So actually documenting acetaminophen in the system is number two, but number three is the presence of very high amino transferase levels, and this, although it's not exclusively limited to

acetaminophen, it's very characteristic as I think you could see.

Certainly there is some overlap with viral hepatitis, but in virtually all of the cases, there was screening out, you know, by routine hepatitis serologies.

So high amino transferase levels, presence of acetaminophen, presence of history of more than four grams is the best we can do. Most of our cases, by the way, would have all three; not necessarily all of them though.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Uden.

DR. UDEN: For Dr. Lee also.

In one of your slides, you had that there's a 68 percent spontaneous survival without treatment. Does that mean that those people survived without liver transplants or how many of those individuals received N-acetylcysteine and were real spontaneous?

DR. LEE: Yeah. Maybe that's a poor word. We mean survival without transplantation, but again, all of them would have reached the threshold of having hepatic encephalopathy and coagulopathy and then recovered. And something like 80 percent or so would

have received NAC, but not all of them.

DR. UDEN: Okay. And excuse me, Mr. Chairman.

And on your summary slide you said 35 percent were receiving antidepressants and 38 percent were receiving narcotics in your series. How many were receiving both, and how many were receiving either one individually?

DR. LEE: I can probe into that, but I don't have it right available.

DR. UDEN: Thank you.

DR. LEE: Thanks.

CHAIRMAN CANTILENA: Dr. Brass.

DR. BRASS: Okay. I have a question for Dr. Senior.

As I think about the basis for risk associated with the ingestion of a given dose of acetaminophen, it seems that two major host determinates would be what percentage of the ingested dose will be metabolized by 2E1 and to the stoichiometric availability of glutathione to deal with the generated metabolites.

And it's the second that I'd like to probe just a little bit with you. Specifically, are there any data in man as to the variability in the

glutathione content of the liver per gram of liver?

And how predictable is that, as well as the relationship between liver weight and body weight and, therefore, the glutathione content for an individual?

So we do not dose acetaminophen per kilogram. So the effective dose in a 50 kilogram person versus a 100 kilogram person might be very different if the amount of glutathione available for detoxification scales by body weight.

So could you just comment a little bit on glutathione content in human liver?

DR. SENIOR: Yeah. These are excellent questions and very pertinent to the problem and really deals with a lot of the previous questions.

What data are available in man? Very, very few on these points that you raise so pertinently. In searching the literature, there are hundreds of papers on acetaminophen metabolism, on acetaminophen absorption. There are scores of papers on glucuronidation, on sulfation, on glutathione conjugation, but very few, very, very few of those papers, only a handful, give data on individual people.

What they give is means of groups, and

what we're concerned about is that some people may lack glutathione stores in the liver, but we don't know it. How would you find out?

Well, you'd have to do an awful lot of liver biopsies or something in order to find out, and that just hasn't been done.

Recall that this drug, acetaminophen, was approved before there was even a requirement to show efficacy so that there were never any really properly dose ranging studies done for safety purposes. And the methods and techniques available in 1950 were very limited.

Now, there are some new techniques coming available now, something called metabonomics, which is an analysis of metabolites, which can be done on very small samples of urine and serum and blood or plasma. And we hope that we can find out something to answer some of your questions.

The key question is how much of the reactive intermediate is formed and is not conjugated to a harmless glutathione mercaptide. It's the unconjugated, freely reactable NAPQI, this reactive intermediate, that does the damage, and the best estimates that were made by Kritchley and Prescott were that there's a huge interindividual variation,

but we don't really have good data in humans.

DR. BRASS: Well, for example, it's often said that the issue with alcoholics is both induction of 2E1 and depletion of glutathione stores. Do we know in man; are there any data as to how much alcohol it takes to lower glutathione and how much it lowers it?

DR. SENIOR: Only anecdotally. We don't have any really systematic studies in man unfortunately. There are some studies. Dr. Watkins and Dr. Slattery, I think, did some studies on giving a rather large single dose of alcohol to naive subjects and showed that there was a modest induction of about 20 percent.

But that isn't the way most people drink. Most people may take two or three drinks a day over a long period of time and thereby may be inducing over a long period of time rather than just over one six-hour period of administration.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. D'Agostino.

DR. D'AGOSTINO: I have a couple of questions I think are directed to Dr. Lee and some of the FDA individuals.

You all admit quite readily the weaknesses

of the databases. So I have two questions that I'm trying to grapple that might give me some more insight.

A number of you mentioned or showed comparisons between the suicidal and the unintentional. Is there some insight I'm supposed to gather by those type of comparisons, number one?

And, number two, on the different databases, could you just review again how you get your final data from those who die in terms of what they actually did take?

DR. LEE: Yeah, I'm not sure I can answer the second one. I'm not sure what you're driving at.

But the answer to the first one is -- could you rephrase the question? I got stuck on the second.

DR. D'AGOSTINO: You gave comparisons between the suicidal --

DR. LEE: Okay.

DR. D'AGOSTINO: -- and the unintentional.

DR. LEE: Right, right.

DR. D'AGOSTINO: And I'm trying to grapple with the notion.

DR. LEE: Right.

DR. D'AGOSTINO: What am I to gain from

those comparisons?

DR. LEE: Okay. I think the difference from, let's say, the Parkland study, for example, is that the unintentional cases, not realizing they've done something in error, do not come in in a timely fashion and, therefore, don't get NAC early and tend to have more severe injury. That is, they tend to have a worse outcome overall, in the overall universe of these kind of patients.

There's many, many more patients that come in very early, suicidal intent, don't even raise their aminotransferase levels. However, of the suicidal cases that reach the level of acute liver failure, they look identical to the accidental cases.

But I think the point is the disease sneaks up on the so-called unintentional or accidental cases.

DR. D'AGOSTINO: Yeah, I'm not sure I know how to make great inferences about the comparisons. I just wonder if all of the suicidals are very successful. You don't see many of them, and you don't know what they took.

The other question about the mortality, I mean, there is the causality that's going on that we're trying to grapple with. If a person dies, you

might list everything that they ever have in their drug chest and every other thing. So could you just go over again how we tied the actual drug intake to the mortality to get that information?

DR. NOURJAH: The mortality data, I go with the coding, whatever the death slide tells me. They coded for acetaminophen. There is a code specifically. I forgot the name. I have it in my document, which when we look at it, that drug, that code primarily exclusively includes acetaminophen, not other drugs.

But for other classifications, for other ICD-9 or E codes I have, they are very general. They include so many different drugs into one class. So I don't know exactly what specific medication they use for overdose, but I know they have overdoses with other class of drugs.

DR. D'AGOSTINO: But on these spontaneous, is it they get the information upon arrival? I mean, is there later review?

You know, if they run to the emergency department, is that where the information is gathered?

DR. NOURJAH: For?

DR. D'AGOSTINO: For any of the databases.

DR. NOURJAH: For any of the database --

DR. D'AGOSTINO: I just don't have a sense of how extensive especially with the mortality cases, how extensive and complete, over complete the data gathering is.

DR. NOURJAH: Well, we know that certificate is not very complete. Whatever the certifier put on the death certificate, we go with that. They may not put all the medication or not at all in some cases.

Now, whatever the list of the medications was and how they do coding I do not know exactly, but I know they have overdose to other medications besides acetaminophen. That's the only thing I know.

And you asked why we did comparison. The reason I compared, to look at, to see what risk factors that these intentional -- the accidental have compared to intentional because we know that intentional or associated deaths, it's related to major overdose. They take so many medications, so many dose of acetaminophen. We know that.

But for unintentional we don't know anything, and we want to know what leads to that hepatotoxicity or death. We don't really know they've got hepatotoxicity or not. What we know, it is on death certificate a mention of accidental overdose to

APAP. And we wanted to know what leads them to death. What other risk factors was mentioned on death that led them to death?

DR. D'AGOSTINO: Thank you.

CHAIRMAN CANTILENA: Dr. Cryer, please.

DR. CRYER: This question is also for Dr. Lee.

In the database review by several of the FDA reviewers, underlying chronic liver disease surfaced as a potential risk factor for acetaminophen related hepatotoxicity, and this certainly caught my attention because my assessment of the previous literature was that chronic liver disease -- it certainly wasn't conclusive that that was related to acetaminophen hepatotoxicity.

So my question is: based upon your database review or based upon your studies, did that surface chronic liver disease as a risk factor and what's your assessment of chronic liver disease as being a potential risk factor?

DR. LEE: We have very little data about that, Byron, because we basically exclude those cases from further consideration. In other words, we try to eliminate acute, nonchronic cirrhosis with superimposed acetaminophen toxicity. That's kind of

our basic criteria.

Not to say that there might not be some cases that didn't have cirrhosis, where they didn't know -- the patient didn't know they had Hepatitis C beforehand, and we certainly do screening, and we will occasionally pick up Hepatitis C antibody, but I would say it's a very low number because our site investigators are already excluding these people from the beginning.

DR. CRYER: Well, can you give me your assessment then just about the possibility or the feasibility of that association, not specifically based on your experience?

DR. LEE: I'm not sure I can. I think it's possible that there's an effect, but every one of the hepatologists in the room is probably still using acetaminophen in chronic Hepatitis C patients for symptoms related to interferon therapy. So I don't think we're excluding people with chronic liver disease from using any acetaminophen at this point certainly.

I hadn't focused in on that, again, because we've tried to separate out and only consider the people that have an acute problem.

CHAIRMAN CANTILENA: Dr. Cush.

DR. CUSH: Dr. Lee, I also have a question. In one of your slides where you looked at acute liver failure patients, you showed antidepressants as a risk factor in about a third of the patients.

DR. LEE: Yes.

DR. CUSH: Can you explain that or do you think that's a surrogate marker for maybe some other behaviors that may have put them on your list?

And did you see a use as a predictive factor in the Parkland study?

DR. LEE: Yes. There seemed to be less in the Parkland study in our unintentional or accidental group, although I don't have the number right available. We were surprised by that, but I think if you reflect on the group of individuals, many of them again having chronic pain, low back pain, they are often seen in a pain management clinic and would be given antidepressants as adjunctive therapy. That's my assumption.

But to exclude the likelihood that a few of them or some of them even have occult suicide ingestions I can't say. And, again, this group may be having a chronic pain problem and then take a suicidal overdose, which might explain, you know, the abrupt

onset of a problem when they seem to have been tolerating four grams or six or eight or ten grams a day.

CHAIRMAN CANTILENA: Dr. Wood.

DR. WOOD: Yeah, this is both a question, I guess, back to Eric's comment from earlier. It seems to me there are three major factors associated with acetaminophen hepatotoxicity. One is the dose or concentration that the patient is exposed to. A second one is the amount of drug going down the potentially toxic pathway, which is mediated by 2E1, and the third factor, I guess, is the extent of the glutathione stores that the individual has.

And part of the question about the intentional/nonintentional is an attempt to convert, I suppose, the continuous variable of dose into some discontinuous variable which may or may not be appropriate.

It seems to me, however, that we all got very comfortable extrapolating from other situations in which we induce or inhibit drug metabolizing enzyme. You know, we label drugs if they're metabolized by a CYP3A as being lightly to be interfered with by other agents that inhibit or induce 3A, and we do that in a fairly confident fashion.

We know a lot about the things that induce 2E1, and all of the animal data points to induction of 2E1 as being an important risk factor for toxicity. It seems extraordinarily improbable that induction of 2E1 in people, given all the information we have, would not also be a risk factor for toxicity.

So I don't see there's a major distinction between labeling for induction of 2E1 for toxicity as acetaminophen as being any different from labeling from inhibition of 3A, which do every day of the week almost.

Going to the glutathione stores is harder. Intuitively, in animal studies there's plenty of data to show that depletion of glutathione increases toxicity of drugs, such as acetaminophen, that are normally detoxified by binding to glutathione.

It's probably also reasonable and relatively low risk in terms of labeling to say that individuals whose glutathione stores were in some way depleted are at increased risk. I don't have data to support that, I guess, but doing that experiment would be hard to do. But it seems an extraordinary low risk labeling issue.

But the focus I think, the major focus, should be on deciding whether we're going to label for

factors that induce 2E1 and identifying in a broad fashion what these are. There may be other enzymes that also contribute, but 2E1 certainly seems a major contributor.

CHAIRMAN CANTILENA: Dr. Clapp.

DR. CLAPP: My question is for Dr. Karwoski.

I'd like to ask whether in your review of the pediatric literature on acetaminophen toxicity, whether or not you were able to ascertain if there were any cases of mortality or morbidity along the lines of children over 12 taking adult doses of acetaminophen, at a four gram per day maximum who are less than 40 kilograms. If you had lightweight 12 year old children taking appropriate doses along the labeling that could result in toxicity of 130 milligrams a day or more.

DR. KARWOSKI: We didn't have any of those specific cases today. The oldest among the pediatric was eight years old. There was one case that was actually summarized in the adults of a 19 year old who was only 26 kilograms and received a dose of 600 milligrams Q six hours and developed hepatotoxicity. This particular woman was also on tegretol, which they thought there might have been some sort of drug

interaction there that resulted in her having an increased susceptibility to APAP toxicity.

But, no, our medication error staff have actually reviewed other databases or data sources where there wasn't necessarily hepatotoxicity associated with it, and they did find a number of times where adult formulations were given to children, but in many of those cases there wasn't a toxicity associated with it.

CHAIRMAN CANTILENA: Dr. Johnson.

DR. JOHNSON: I have a question for Dr. Lee.

In one of your slides you describe that 38 percent of the unintentional patients were taking a narcotic combination, and I'm wondering if you have data on whether the high doses of acetaminophen were the result of taking the combination product plus over-the-counter acetaminophen or was really sort of a side consequence of abuse of the narcotic product.

DR. LEE: I don't have that specific data. I think the majority of them were more abuse of the product, in other words, taking a daily dose that was in excess of four grams, but there may have been -- I just don't remember offhand how many were actually double use individuals.

CHAIRMAN CANTILENA: Dr. Day.

DR. DAY: I have a question for Dr. Karwoski.

In the overall summary from the Office of Drug Safety, three broad classes of factors were cited, factors concerned with the product itself, with knowledge, and with risk factors, and we've heard a lot this morning about the product and about the risk factors.

And can you comment on the knowledge component, specifically the availability of research studies on prior knowledge about potential toxicity and also any label comprehension studies which speak to this issue, and in both consumers and health care providers?

DR. KARWOSKI: I'm not going to be able to comment on that. I'm not aware of that. I'm not sure. Somebody else from the OTC Division might be aware.

CHAIRMAN CANTILENA: Yeah, I think we'll have an opportunity this afternoon to talk about that a little bit.

Okay, and Dr. Alfano.

DR. ALFANO: My questions is for Dr. Lee.

Dr. Lee, you've assembled an admirable

network of study sites and are doing prospective work in this area. I think it's the only such database we've heard from, and it may explain why the bulk of the questions have been directed to you today.

In his introductory remarks, Dr. Ganley indicated that the FDA has not had access to this data. Since your studies are ongoing and since this problem clearly will need to be evaluated on an ongoing basis, my question is: is it your intention to make this data available, raw data available?

DR. LEE: Yes.

CHAIRMAN CANTILENA: Okay. Thank you.

Two more questions. Dr. Katz, did you have one? And then Dr. Uden, and then we'll close.

DR. KATZ: Thanks.

I just wanted to follow up on the issue of causality for anybody who'd care to answer. It seems like from a fundamental epidemiological standpoint we're a long way from deducing causality from the data that we've seen, which was just really associations. And one would normally think of doing at least a case control study where you try to get around the issue of that when people get sick, they start to take whatever is in their medicine chest.

And one could easily see that if you

developed any painful illness, meningitis or what have you, they'd start to take whatever was in your cabinet.

So I wonder if anybody is aware of any case control data where people were hospitalized for other serious illnesses or looked at for how much acetaminophen they were taking, whether they were taking multiple formulations, whether they were taking high doses to see whether, in deed, there is any strong reference for causality in some of the cases we've seen, especially with the levels of therapeutic dosage of acetaminophen.

CHAIRMAN CANTILENA: Who from FDA would like to answer that?

DR. BEITZ: We're not aware of such studies.

CHAIRMAN CANTILENA: Okay, and then our final question for this part of the program, Dr. Uden.

DR. UDEN: Yeah, I'd like to nail down the pediatric mortality information. In the presentation by Nourjah, Ahmad and Karwoski, they talked about age. Some of you alluded to it, and Karwoski, you had information about pediatric deaths.

I remember back in the late '70s, early '80s. I don't know how commonly this was held that it

was children less than six or infants. Really if they took an overdose of acetaminophen, there weren't really any published deaths at that point in time, and that for some reason that they were able to metabolize a drug more efficiently better didn't have the toxic intermediate.

So what do we know about pediatric patients less than six years of age and their risk for mortality as compared to risk of mortality of the group who are in their 30s, 40s, and 50s?

DR. NOURJAH: From my observation from these databases, if you look at the pyramid, I mean, I didn't create the pyramid for children less than six. However, we have a lot of observation visits for children less than six to come to emergency department, and then less so go to hospital, and for mortality data, they're a very small number, very, very small number. Like it's like suggesting their children, although they get overdose to APAP, but the severity is not that much.

That I can tell from the data I see.

DR. UDEN: And that's all we know about that? It would seem that we would know a lot more about pediatric mortality related to acetaminophen than that. I mean, I'm just surprised at that.

DR. KARWOSKI: I don't think the spontaneous reports are going to give us that answer. I mean, we certainly have a smaller number of reports in pediatric which may give you some indication that they seem to run into trouble less often, but we can't make any comparisons as to the mortality in those versus adults.

CHAIRMAN CANTILENA: Okay. Thank you.

I think what we'll do, I first of all want to again thank the speakers from the FDA for their presentation. We'll now take a 20 minute break.

(Whereupon, the foregoing matter went off the record at 10:07 a.m. and went back on the record at 10:34 a.m.)

CHAIRMAN CANTILENA: We're going to begin the open public hearing session, and the first group that will be presenting will be led by Dr. Bowen. Dr. Bowen? And this group has five, zero minutes, five, zero minutes for their presentation.

DR. BOWEN: Good morning. Mr. Chairman, Dr. Galson, Dr. Ganley, advisors and consultants and FDA, I'm Dr. Debra Bowen, Vice President of Research and Development at McNeil. We are the primary researcher and manufacturer of acetaminophen, which is the most widely used analgesic in the United States.

McNeil also markets ibuprofen and aspirin products. It's a pleasure to be with you this morning discussing the science of the safety of our products.

As you know, McNeil's overriding commitment is to our consumers who use our products and to the health care professionals who recommend them.

Today our objective is to provide a context for the committee's consideration around questions raised by FDA. We'll provide the scientific evidence that acetaminophen is safe and effective as it is currently marketed and formulated, and we'll also review the data and the databases that underscore acetaminophen's safety and use.

We'll share information about some actions that we've taken to insure that acetaminophen in actual use continues to be one of the safest drugs available when taken as directed.

Let me begin by providing a brief background on acetaminophen. In the United States, acetaminophen has been marketed since the '50s, and it's used by more than 100 million people each year. It's also used in culturally and racially diverse populations around the world.

Instances of serious harm are rare,

although we are the first to say that we must insure its safety and use.

As you know, all drugs have risks as well as benefits. In massive overdose, 15 grams over a few hours, acetaminophen may cause hepatic damage if N-acetylcysteine, NAC, isn't administered early.

In adults, most of these episode are suicidal. In children, most are accidental ingestion. Our review of the 307 AERs cases suggest that rare serious adverse events may occur in American consumers who inadvertently overuse acetaminophen containing products.

That is the issue that we're here today to discuss with you. The precise incidence of harmful, in advertent overuse can't be accurately determined from the databases that we currently have. It is clear, however, that given the fact that 48 million American adults use acetaminophen containing products in any single week, it is a rare event.

The reasons for inadvertent overuse are even harder to uncover. We've reviewed the case reports containing incomplete or inaccurate descriptive information, and we've coupled this with our understanding of reported consumer analgesic use patterns to reveal actionable insights.

To reach actionable conclusions, we reviewed and discussed with scientific experts the science of analgesics, acetaminophen and the NSAIDs. We initiated a new multiple dose pharmacology study to gain additional insight.

This study provides new data that you'll be hearing later, underscoring this drug's wide safety end use margin.

We also conducted a modern dose ranging efficacy study to confirm findings in old studies that the optimal single adult analgesic dose is one gram.

In addition, we looked at consumer attitudes and behavior. In cases where consumers report product overuse or misuse, we set out to better understand the attitudes about medicating that may underlie their reported usage.

Now, McNeil's interventions fall into two categories. First, interventions intended to prevent serious adverse events from drug overdose.

Second, interventions to optimize appropriate use. McNeil has always taken the leadership role to insure the safety and use of acetaminophen containing products for all consumers, not just those who buy Tylenol.

To prevent serious adverse events in the

case of large drug overdoses, McNeil initiated the IND for the antidote, NAC, funded the support of its development, provides continuing support for Poison Control Centers to answer overdose inquiries, and introduced a child resistant and error resistant concentrated drop device for infants.

These are all examples of our longstanding commitment to prevention of drug overdose and safety end use for American consumers.

FDA has focused today's dialogue on unintentional misuse. We have implemented labeling changes that build in the strength of FDA's Drug Facts label to further minimize the inadvertent overuse of analgesics and today we are recommending an organ specific overdose warning.

These labeling and education initiatives are equally relevant to the other over-the-counter drugs that we market, including ibuprofen and aspirin and all multi-symptom analgesics.

In addition, we continue to emphasize the importance of our citizens' petition to allow dosing directions for children under two years old on infant's products. We believe with you that the American consumer is smart, responsible, and can self-manage medications.

Because our time is limited, we'll use the remainder of our time to review the science of acetaminophen. We strongly encourage the committee members to come by and review our intervention programs in more detail down the hall in the Potomac Room.

We look forward to the discussion this afternoon.

Today my colleagues will review the longstanding science, new data, and provide their own points of view for your consideration. Dr. John Slattery from the University of Washington will discuss the pharmacokinetics and metabolism of acetaminophen and will present the recent multi-dose data.

Dr. Richard Dart, Professor from the University of Colorado will review clinical toxicity overdose and case analyses.

And Dr. Raymond Koff from the University of Massachusetts will discuss issues in special populations focusing on underlying liver disease.

And finally, Tony Temple, Vice President of Medical Sciences at McNeil will complete our presentation and direct the question and answer session.

Our review supports key conclusions, namely, that acetaminophen has been marketed for over half a century worldwide and in many populations. Review of science and consumer usage continues to underscore its safety. Harm is rare and is caused by overdose.

Serious harm, caused by inadvertent misuse, is very rare. As manufacturers of acetaminophen, ibuprofen, and aspirin, proper consumer use of the entire class of pain reliever fever reducers is our objective. Any change in effectiveness due to lower a dose, changes in access, or risk emphasis for one ingredient in the entire analgesic class will affect consumer choice and health outcomes.

Today we welcome the opportunity to share what we know and to learn from you. Making the right changes, affecting consumers' health in an overall positive direction is a goal that we share with you.

Thank you.

Dr. Slattery.

DR. SLATTERY: Thanks very much. It's a pleasure to be here today to talk with you about a compound that I've been working with for 20-some years.

You've already seen a review of the metabolism of acetaminophen, but that's actually what I'm going to be talking about in relation to hepatotoxicity, and as you've heard, the majority of the dose of acetaminophen is actually eliminated by nontoxic routes to the formation of a glucuronide conjugate and a sulfate. There's a relatively small fraction of the dose, a few percent, on the order of five to ten percent of the drug that's converted primarily by Cytochrome P450 2E1 by two reactive quinonimine called NAPQI, and this exerts toxicity by binding covalently to macro molecules and also initiated processes, such as oxidative stress.

Under normal circumstances this, of course, is conjugated by glutathionate transferase enzyme with glutathione to form the glutathione conjugate, which is eventually eliminated in the urine and cysteine mercaptor (phonetic) acid conjugates and other thiol ethers.

It's important to realize, and as you've heard today, as the dose of acetaminophen is increased a couple of things happen. One is that the co-factor for this process becomes depleted and you have less going out by this route.

And another thing that happens, of course,

is the glutathione stores within the liver become depleted, and we end up with more of this reactive intermediate being available to covalently bind and eventually cause toxicity in the liver.

So the important things to remember from this is that there is something of a threshold phenomenon here and that you have to deplete those co-factors. When we look at glutathione stores, we have to have substantial depletion of glutathione stores before we get appreciable hepatotoxicity.

And, of course, we'll remember here that acetaminophen is nontoxic at recommended doses.

Now, there is a little bit of controversy in the literature regarding the enzymes that are responsible for the oxidation of acetaminophen to the reactive species NAPQI, and those enzymes in the human that have most often been talked about are 2E1, 3A4, and 1A2.

And the evidence for this largely comes from studies in human liver microsomes, and this is just some data from our own laboratory, and the way that this works is that it's called reaction phenotyping, and one uses various chemical inhibitors very often that are specific for certain isoforms, and you look at the degree of inhibition.

Here we had just 35 percent inhibition in this human -- the microsomes from this human liver at a dose or at a concentration of acetaminophen of 0.1 micromolar.

And I won't go through the rest of this in any detail, but as you know, those of you particularly who have dealt in this area of drug metabolism with Cytochromes P450, in vivo or in vitro to in vivo correlations are not always perfect.

So a few years ago we started some studies, and we were particularly interested in probing the contribution of 1A2, and the way that we approached that was through a drug interaction study using omeprazole, which in slow metabolizers of mephenytoin -- those are deficients in 2C19 activity -- achieve high levels when maximum daily doses are used.

One of the things that we included in this study as a positive control was caffeine. Caffeine, as you know, is a probe substrate for Cytochrome P450 1A2. The important data to look at is over here with the slow metabolizers, and what you can see is that in the presence of omeprazole, the caffeine clearance was almost doubled.

By contrast, when we look at the formation

clearance of these thiol ether conjugates, this is actually a measure of the ability of the individual or the body to form NAPQI. You can see that that formation clearance actually didn't change, and this then suggests, it shows us that P450 1A2 is not important in human beings in making this intermediate.

This is important when one thinks about risk factors. Smoking can kind of be rules out at this point and other compounds that would induce 1A2.

When we saw this, we thought that we'd better continue with this series, and we conducted a study of rifampin again on the disposition of acetaminophen. Now this study was conducted very much the same way. Rifampin is recognized as a very potent inducer of 3A4.

And what we did here, again, it's a relatively small study. We administered rifampin, 600 milligrams per day for seven day, again looking at this measure of the ability to form the reactive intermediate.

We can see between the minus rifampin case and the plus rifampin case there was really no difference in the ability to form that. So that in vivo in human beings, 3A4 seems not to be important in the formation or NAPQI.

This then also rules out another potential set of drug interactions. So we thought we had better continue on this line, and the next approach that we took was we used disulfiram, which is a very potent inhibitor of Cytochrome P450 2E1, and here we gave disulfiram 500 milligrams the evening before the individual received acetaminophen, and again we have this same measure of the inability to form the reactive intermediate.

And what you can see is that this actually declines substantially. It actually declines by about 75 percent. So only 25 percent residual activity to form NAPQI was left.

And so what this has told us and my thinking has been from that time that P-450s 1A2 and 3A4 are not important in human beings, live human beings in forming the reactive intermediate from acetaminophen, but the 2E1 is by far the principal enzyme in that process.

So as I said, it has important implications with regards to drug interactions. The issue of drug interactions and particularly inducers of 2E1 has been brought up earlier this morning, and one thing I would like you to know is that the mechanism of induction of 2E1 is kind of different

than with most other P450s, at least one particular facet that is important.

One of the ways that this -- this is 2E1, in case you can't recognize the shape of this protein here -- present in this little cartoon, had what we're considering here is a substrate. We can think of the substrate being acetaminophen, and we have an inhibitor inducer and probe inhibitor inducers that we've done studies with are isonized in ethanol.

And the way that this works is when this inhibitor inducer -- and you'll see in a minute why I call it both -- is present, it can bind the active site. Okay? It's just -- all it needs to do is be a ligand for 2E1. It bind the active site, and when it does that, it protects the enzyme from degradation.

So what you see here in the cartoon is now two molecules of this enzyme, but the important thing to realize is that while it's been induced, protein levels are up. The active site is occupied so that the substrate can't get in there.

While the enzyme levels are up during this phase of induction, what we actually see in terms of activity is inhibition because of the occupation of the active site. It switches to enhanced activity when we can see the evidence of induction once the

inhibitor inducer is actually eliminated and the substrate can gain access to that active site.

Now, we've done a few studies that have actually looked at this in humans, and this is a study that was done with Kent Mole and Paul Watkins, who is here today, and in this case what was done was to give ethanol by constant rate, constant IV infusion to maintain concentrations of 100 milligrams per deciliter for a period of six hours, and what we're really trying to simulate here is the folks, you know, who goes out Saturday night, puts the elbows on a bar and has a few drinks, and gets legally drunk and hopefully calls a taxicab and goes home.

What happens during the period that they are drinking, this is the ratio of the ability to form NAPQI at any particular time along this axis, divided by the ability to form that at time zero before any ethanol was initiated.

While ethanol is on board, actually enzyme levels are rising a bit, but what we see is inhibition of the ability to form this toxic intermediate. Once you remove, you stop administering the ethanol, and we see the same sort of thing for isoniazid. The ethanol is eliminated, and as you administer acetaminophen again after ethanol is eliminated from the body,

that's the time at which you can actually pick up the enhanced activity.

There's a thing that's important to realize about this interaction, and that is kind of the window of vulnerability is actually kind of relatively short and requires that the inducer-inhibitor administration actually be stopped.

There were some questions about what goes on with hepatocellular glutathione during this period. We've recently completed some studies that have been accepted for publication, and I can talk about that in the question and answer period, but actually what's going on there in terms of risk of this interaction runs opposite to what's actually going on with the enzyme.

This is a very intricate drug interaction and one that I've been pondering for quite some time.

Another thing that has come up recently in the discussion about risk factors for toxicity following ingestion of administration is Gilbert's Syndrome, and this is a genetic deficiency in a particular glucuronal transferase. The enzyme that's involved in making this nontoxic glucuronide metabolite or conjugate. This is actually a deficiency in UGT 1A1.

Work by Court, et al., published in JPET a year or so ago actually demonstrated that UGT 1A6 is the predominant form in making acetaminophen glucuronide. It has a Km of about 2.2 millimolar, and if we transfer this Km into body burden so that we give it an amount sort of measurement, that really corresponds to a body burden of about 20 grams. So this has a very high Km.

They also identified that 1A1 and 1A9 are minor contributors. So the question come ups really if UGT 1A1 is gone, what is the effect on actually the formation as was identified this morning.

One of the important things in terms of toxicity is the flux of acetaminophen through the NAPQI pathway and how much NAPQI is made. So we can actually calculate that from data that they've presented in this paper.

They did some incubations at half millimolar acetaminophen, which really corresponds to about a five gram body load, and if we calculate that UGT 1A1 actually was not present or its activity was zero, the formation of NAPQI increases to where it would count on average in individuals from about six and a half percent of dose to only about 7.3 percent of dose.

Now, these are studies in human liver microsomes. In these same sets, 56 sets of human liver microsomes, each prepared from a different individual. The overall variability and formation of acetaminophen glucuronide was about 15-fold.

Let me tell you that these conclusions about UGT 1A1 and 1A6 are consistent with in vivo data in people with Gilbert's Syndrome. There have been two studies done, neither has demonstrated that there's any difference in the ability to form acetaminophen glucuronide. So I think this is a strong conclusion.

McNeil has recently conducted some multiple dose studies looking at the super therapeutic range and what the focus of these actually was, is the dose dependence at steady state after the drug has been given for three days.

These studies had 12 individuals per group in the active arm, and they included a placebo arm so that they could follow liver enzymes, and over the period of administration of acetaminophen and three days after the period of administration, there was no evidence. None of the liver enzymes were increased beyond the normal limits.

This is just the acetaminophen

concentration time course, and there's not too much to point out here, except that you'll see really an absence of accumulation of acetaminophen over the period of administration, and we're going to be looking at data as a function of dose really from the last dosing interval of administration.

And so here we have the four gram, the six gram, the eight gram dose, and what we're looking at first is just the fraction of dose excreted in urine, and you're of course interested in this because the fraction of dose excreted in urine as the thiol ether conjugates -- that's what the T is here in each one of these things -- is actually giving you the information about flux through the NAPQI pathway.

These data, these are actually kind of the raw data here, and what's easier to look at for the relatively -- changes compared to what you would see at the four gram is actually these. So these are just these different data sets expressed relative to what happens at four grams.

And what you see at six grams and eight grams is a modest increase in the ability or in the urinary recovery of the glucuronide conjugate. You see a decrease in the recovery of the sulfate conjugate, and that's really expected because we know

that the co-factor for sulfation is being depleted as we encounter doses in this range.

The actual recovery of the thiol ether conjugates that are formed through the NAPQI pathway is decreasing. We have variable results with regards to the recovery of acetaminophen in urine, which is not surprising. The poor solubility of acetaminophen in water makes it renal clearance urine flow dependent. So that finding isn't surprising.

To get a little bit of mechanistic information from this and interpretation, we need to look at what's going on with formation clearances. Formation clearances being the measure with each one of these different steps, the glucuronide, the sulfate, the thiol ether or NAPQI, and acetaminophen renal clearance. This is really a measure of directly kind of what's going on with the activity in those different pathways.

We see something of an increase in the ability to form the glucuronide conjugate, and this is really something of a surprise to me, and I don't have much to speculate on mechanism of that right now.

A decrease in the ability to form the sulfate conjugate, which again is not surprising, and a decrease in the ability to form the thiol ether

conjugates.

There are potentially two explanations, I think, for this mechanism. One is that we know as larger doses of acetaminophen are ingested we deplete glutathione, and that's one potential reason for the decreased recovery of these kind of daughters of NAPQI.

The other is that, of course, we're forming this reactive electrophile that likes to bind proteins, and we know from studies in animals, some conducted in our laboratories and some elsewhere, that NAPQI is actually good at destroying the enzyme 2E1 that makes it, and so there are probably two mechanisms underlying that, one being chronic administration resulting in destruction of the enzyme that actually makes NAPQI.

These interpretations have to be regarded as hypothetical because they haven't yet been directly investigated, and they amenable to experimental investigation.

In summary, NAPQI is formed by Cytochrome P-450 2E1 and modulation of other Cytochrome P-450s is unimportant, in my view, as risk factors in the toxicity of the compound.

Toxicity follows substantial glutathione

depletion, and the mitochondrial pool is -- I didn't have a chance to discuss this very much -- but it's very important in terms of this toxicity.

Absence of UGT 1A1 in Gilbert's disease is not a significant risk factor. We saw that acetaminophen does not accumulate on multiple doses up to about eight grams, and I just mention the changes that actually go on in metabolism.

Thank you very much.

DR. DART: Good morning. I'll be talking about the safety of acetaminophen from several different perspectives. First we're going to talk a little bit about acute substantial acetaminophen overdose. We'll talk a little bit about the AERs data sets and evaluation of those; chronic alcohol use, where we've done some research at Rocky Mountain; and finally, we'll be talking about repeated -- and this is new data on repeated supertherapeutic ingestion also from our poison center.

Well, you just heard that you can give multiple doses of eight grams a day to patients and not have accumulation or liver injury. So you won't be surprised to hear that there are prospective data about acute single ingestion of acetaminophen up to 9.1 grams that show the same results, and because that

data is now available, I'm going to skip over the rest of the slide.

Now, in the clinical situation, we deal with this. This is a tool that we use called the Rumac NAC Nomogram, and what you see here are two lines. One is called the possible liver toxicity line, and the other is called the probable liver toxicity line.

And in the United States, if your serum level after a single acute ingestion falls above the dotted line here, then you will be treated with NAC, N-acetylcysteine.

In the U.K., they use the higher line. So there's a little bit of difference, but the main point of this slide is to show what happens at a therapeutic dose, such as 15 milligrams per kilogram, a common therapeutic dose, and you can see that levels top at about just under 20.

If you take five times that much or 75 milligrams per kilogram, then you can peak out in the range of 90 micrograms per mL, but still far below. So it takes a really remarkable ingestion to get up over the nomogram line.

Now, moving to the AERs data set, this has already been described. I won't go into detail. We

know that it's hepatic events that we're being assessed. There was 307 reports, and we're going to focus on the 281 adult reports. There were also 25 pediatrics and actually one that doesn't mention acetaminophen.

Some limitations like this were already mentioned, but I just want to remind everyone that there are limitations to case reports. We sometimes have to use them in medicine, but really we need to understand that causality cannot be ascertained using retrospective data, especially case reports, for several different reasons, one being the history of dose is often inaccurate.

There's a very strong -- and as a practicing person who takes histories from these patients -- there's a very strong emphasis or pressure on the patient to minimize the dose they have taken. They're in your emergency department. You are seeing them. They very consistently under estimate the dose that they have taken.

The other option is they don't know at all because they're unconscious or intoxicated, and you're just not sure what that history is.

Another concern I have with the case report data is that -- and this is often unrecognized

-- that in today's world -- this wasn't true when I trained, but it is certainly true today -- is that there is very strong pressure from training programs and from hospitals to not put information about suicide in the medical record.

The only time we -- in fact, we counsel our residents: do not put that information in the medical record unless it is extremely clear that this happened because you are going to deprive that person of medical insurance in the future possibly. You may deny payment for their health expenses in the future of any kind. So there's huge implications for the patient to write that in the record, and unless you're sure, then you're not going to put it in there.

Now, we formed an expert review panel that was supported by McNeil. I was the chairman, and these are the individuals that were included in that panel. Several are in the room today, and you can see that they represented emergency medicine, toxicology, hepatatology and pediatrics.

What we did was took the AERs database for adults, 281 adults, met, went through our own self-created panel training and creation of a standardized data collection instrument by the panel.

The panel then reviewed each of these

cases individually and came to their own clinical judgment. In other words, they were asked to look at the AERs report, and based on that data, and obviously there is no other data besides what's in the AERs report, to make a clinical judgment of causality related to the liver injury of that patient, if liver injury was present.

So the panel then met to undergo an iterative consensus process where the group assigned probability of association with acetaminophen. So each person made their individual judgment. Then we met and put these into definitely acetaminophen related probably, which meant greater than 51 percent clinical probability that the liver injury was acetaminophen related; possible, which was less than 50 percent and basically meant that there was another cause that was as or more likely than acetaminophen; unlikely meant -- I'm sorry. I got carried away.

Possible meant less than 50 percent. Unlikely meant that there was another cause more likely than acetaminophen. And definitely not meant there was no possibility in the panel's mind that this was a acetaminophen case. And then the category of insufficient information.

This shows the results of the panel's

deliberations. As you can see, there were three cases that the panel thought were definitely acetaminophen, but if you add those to the probables, then about 25 percent of all cases were considered related. Acetaminophen was considered to be causally related to the liver injury that the patient experienced.

At the other end of the graph, we have the insufficient data, and here we see that about another quarter of the patients, there just wasn't information to be able to make that determination.

Twenty-seven cases were judged definitely not and 53 unlikely. These mean that there was either very good evidence that it was not acetaminophen or another cause, and that accounts for about another quarter of the cases.

And then finally there's this somewhat gray zone of the possibles, where the probability was just judged clinically, and this is somewhat subjective, to be less than 50 percent

If you look at these in a little more detail, what you see is that most of the definite or probable cases were associated with substantial overdoses. That's not surprising at all.

Also, most of the definite or probable cases were also associated with alcohol or alcohol

abuse, although as the FDA also noted from theirs as well, this is spontaneously reported. So we really don't know what the incidence of alcohol abuse was in the groups.

Finally, I'll just mention the 25 pediatric reports. Four were unintentional single ingestion. There involved a maternal overdose, and 18 involved administration. Most reported children under the age of two years, which is one of the reasons that that would be nice to have on the label.

Now, out of this information the packaging or the materials for this meeting lists putative risk subsets, especially history of liver disease, coingestion of hepatotoxic medications and ethanol use.

Now, there's several concerns here, the primary being that this is all based on essentially case report data, and so this is very soft.

The other problem is that acetaminophen, as we've heard, is used in about 23 percent of people in an given week or 100 million individual users per year. So there's a huge confounder here in that if I'm going to die of something and I happen to have taken acetaminophen, the presence of acetaminophen in the blood in a person who is dying does not indicate

that it was -- or even in liver injury -- does not indicate that the acetaminophen was the cause of that liver injury.

There's over 100 substances just on a short list that are known to cause hepatotoxicity to levels greater than 1,000 on AST. So there's a huge confounder here.

And then finally, on the ethanol use, I'd just like to present some data that we've generated in Denver. We performed a randomized, double blind, placebo controlled trial in hard core alcoholic patients. These patients received acetaminophen, one gram, or placebo four times daily for two consecutive days. These were all currently drinking alcoholics by history. Over 50 percent of them had been doing this for over 20 years, and nearly all of them had been doing it for at least five years.

One third of the patients had a low body mass defined as less than 21. Standing here, my body mass is 26.

We found that there was no statistically significant difference in the mean AST, ALT, or INR at two and four days for the acetaminophen group, and we're doing another study that's similar. We've enrolled 80 patients and have the same results.

Now, I want to point out that if you remember Dr. Slattery's slide where you saw the biphasic effect of alcohol, what we do in these cases is the patient comes in intoxicated. We wait until the alcohol wears off, get informed consent, draw their blood, administer the acetaminophen.

So we're administering the acetaminophen at the time of maximal vulnerability for that patient.

Jumping quickly, and I'm sorry to switch gears so fast, I'd like to talk about repeated super therapeutic ingestion. What do I mean by that?

Well, that's our term for the patients who take multiple doses throughout a day or usually more than a day that amount to more than four grams in a day. So they're taking more than the recommended, but they're doing it split up, not as an acute single ingestion.

We see a lot of acetaminophen. We had in this 16 month period 7,300 cases of acetaminophen. That's because we are well known nationally for this and get a lot of phone calls about it.

Of those 277, we had a documented history of repeated super therapeutic ingestion as I just defined. Two hundred forty-nine patients agreed to be enrolled in the study, and in those patients we

measured their acetaminophen level and their AST level or recommended that to the physician calling, I should say.

If either of those was positive, greater than ten or greater than 50, that patient was treated for at least 12 hours with acetylcysteine. If not, they were discharged.

But the important point here is that we then followed them up over the subsequent 72 hours, and here's the results of that study.

For patients who had no liver injury, and that means upper limits of normal; so they were underneath the upper limits of normal for the person's lab that was calling. There was a mean ingestion of 10.6 grams with 95 percent confidence intervals of 9.4 to 11.7.

There were 126 of these patients. One hundred nine were completely well at follow-up. Seventeen were lost to telephone follow-up. However, they were well when they were discharged from the hospital.

In the group that achieved AST levels of 50 to 1,000 international units per liter, the mean ingestion was 11.7; confidence intervals of 9.6 to 13.8. There were 40 of these patients. Thirty-seven

did well, and three were lost to follow-up.

Among patients -- and this is probably the most interesting group -- that achieved ASTs greater than 1,000, sort of the traditional definition of acetaminophen induced hepatic injury, 12.6 grams was the mean dose, 10.3 to 14.9, and I want to point out this relationship here where there was a striking increase in the duration of the ingestion as the enzyme levels went up.

There were 44 patients in this group. Still 37 of them did well. However, seven of them -- actually six died and one was transplanted for a total of seven patients.

The not done group means that this is where the physician did not draw the laboratory test that we recommended, and as you can see, they tended to be -- basically they weren't ones he expected to get toxic. They were lower doses, and they did -- every one we followed up did well.

They probably belong in this group, but we separated them out because we don't have that AST level.

Looking at this data graphically, you can see that we see a dose response relationship for -- there's no toxicity in this column. Mild to moderate

I guess I would call this, and then greater than 1,000 in this column.

And especially I think the time is something that we -- it's very striking to us in handling these cases, is this isn't something that happens in one day. This takes kind of a committed effort. I'm not saying they'd necessarily do it intentionally, but there's really -- it takes some time to be able to develop this.

Switching gears again, I'm going to talk about the data from the submission about acetaminophen associated. It was called acetaminophen related in the packet. I've called it associated because I felt that was a better term, and they're talking about a total of 458 deaths from acetaminophen each year. This is an annual figure.

Now, something that's worrisome about this data is, as Dr. Lee mentioned, this is -- you know, patients who have acetaminophen toxicity have some very characteristic things, which is they always have liver injury if they're going to die during that acute event.

And yet on these discharge summaries, even though these patients should have had severe liver injury, no liver disease was reported.

So we're not sure what to do with that section of the data. This includes hepatitides and things like that. This is the chronic liver disease, and then there were 58 patients out of that that were acute liver toxicity.

If you look at those 58, 28 were stated to be unintentional, 30 intentional. Even this number concerns me because of the fact in medical records that it's so common to not write down intentionality or suicidality at least because of the ramifications for the patient.

And that's not one we're going to cover for time.

Conclusions. Prospective studies to date indicate no toxicity at or near the recommended dose of acetaminophen. Serious hepatotoxicity does occur. The single does estimate, as we've heard before, is 15 grams or, as emerging evidence is showing, it appears to be about 12 grams a day for repeated dosing.

Our alcoholic data suggests that alcoholics may safely take the current recommended doses of acetaminophen, and therefore, I see no need for any dose reduction.

Thank you.

DR. KOFF: Good morning. My name is Ray Koff. I'm a hepatologist.

I want to address some of the questions that came up this morning with regard to the safety of acetaminophen in patients with chronic liver disease.

Acetaminophen at currently recommended doses, up to four grams per day, is safe to use in patients with chronic liver disease. And the supporting evidence from this comes from prospective, single dose, and multiple dose studies in a variety of liver diseases: chronic hepatitis, cirrhosis, alcoholic liver disease, metabolic liver disease.

And finally, there is a large clinical experience over the last ten years in the use of acetaminophen in patients with chronic liver disease.

In contrast, as you've heard this morning, the concerns for increased hepatotoxicity at therapeutic doses of acetaminophen is largely based on anecdotal case reports which may be inaccurate, may be unreliable, and it's very hard, I think, to use them.

Now, this is not a new subject. Studies of acetaminophen metabolism in patients with chronic liver disease go back more than 20 years. Here's a study by Forest and colleagues, 1979, looking at patients without liver disease, patients with mild

liver disease, patients with severe liver disease, based on synthetic liver function.

These were given a single dose, 1.5 grams of acetaminophen. Urinary metabolites were looked at, and although plasma half-lives were, in fact, prolonged in the patients only with severe disease, urinary metabolites did not change, suggesting that at least that dose given in a single time period had no effect on hepatic metabolism of acetaminophen.

I'll skip that one.

Gordon Benson, who's sitting in this audience did what is a landmark study also almost 20 years ago. He took a group of stable patients with liver disease, most of them who were biopsy proved, some with cirrhosis, some without cirrhosis, and gave them four grams of acetaminophen or placebo in a double blind crossover study.

And what he showed is that the typical markers that we look for for hepatotoxicity, bilirubins, bilirubin fractionation, AST and ALT, did not change with almost two weeks of therapy.

Now, the most common use today for hepatologists in 2002 is the use of acetaminophen in the management of patients with chronic Hepatitis C. This is what we do day in and day out.

Dr. Dargere and colleagues in France, realizing this and understanding the bits of controversy about this, decided to use three grams, which was the recommended threshold in France -- it's now four grams, by the way -- in a study of 17 patients who received placebo, 17 acetaminophen, for a period of one week.

And as you can see, looking at ALT as the most sensitive marker, there were no changes either at the end of the therapy and three days later in the placebo versus the acetaminophen group.

Because these patients did not get interferon, there was no change in antiviral -- in viral levels, and one would not expect changes in viral levels with an oral analgesic.

Now, we've had, as I mentioned in the beginning, over a decade of experience using acetaminophen to manage the side effects of interferon.

In February of 1991, the FDA approved for non-A, non-B Hepatitis/Hepatitis C interferon alpha 2B. The starter packages that Shering sent out to treating physicians contained not only interferon alpha 2B, but acetaminophen.

Today we are now using pegylated

interferons, and Dr. Lee and myself, Dr. Riley in the back, and every hepatologist who is in practice today continues to use acetaminophen to manage the side effect of the pegylated interferons.

We monitor these patients exceedingly carefully. We bring them back at week one, week two, week four, week eight, week 12. Every month we see them, and they are on extended therapy for upwards of a year and sometimes longer. We see no evidence of hepatotoxicity.

Finally, if you're a physician dealing with patients with liver disease, you understand that thrombocytopenia is an important problem in those with hypersplenism and cirrhosis, and this agent has no impact either on platelet number or platelet function.

So at recommended doses, acetaminophen for hepatologists remains the analgesic of choice, and I think no dosage adjustments are necessary in patients with liver disease or those who have liver dysfunction.

Thank you.

DR. TEMPLE: No, I'm not Dr. Carr. We're going to pass through is presentation.

Good morning. I'm Dr. Anthony temple. I'm pediatrician, medical toxicologist. I know quite

a few of you. I wish I knew more. That's sincere.

I'm pleased to be here. This process has been a great opportunity to review the wide array of medical literature, case reports, and new research about acetaminophen.

And what I would like to do very quickly, and just provide you a summary of the data we've talked about. You got a huge submission from us. I hope you got a chance to read it.

What we think are the implications of that data, and then maybe ask some questions that we also think need to be considered in this process.

There's no question but what acetaminophen has been extensively investigated. Thirty thousand research articles have been published on acetaminophen, 30,000 research articles since 1970, but sometimes the science is not always fully understood, and that's why we have discussions like this.

And there are a couple of things that we think need to be emphasized then. One is that the threshold effect associated with the risk of overdose toxicity, is it really an important consideration.

You have to exceed the threshold in order to have toxicity, and it's a secondary effect. It is

the depletion of 70 to 80 percent of hepatic glutathione before toxicity occurs, and data demonstrates that it takes a substantial overdose to do that.

We have shown you studies involving administration of single, large doses well in excess of the recommended dosage range, as high as nine grams, but do not cause toxicity; a dose escalation PK study with doses of four grams per day -- that's the recommended dose -- plus six grams per day, plus eight grams per day, given for three days without any adverse events or alteration of metabolism of acetaminophen or the events of liver toxicity.

And, in addition, even though the data are still case reports and have some or all of the difficulties that case reports have, Dr. Dart's prospective case series of repeated supertherapeutic ingestions, where an added effort has been made to quantitate the doses in which it gives us probably the best picture, I think, of risk from repeated supertherapeutic ingestion, and that suggests that it takes doses in the range of 12 grams per day over several days to produce significant toxicity.

Now, much has been said about individual case reports, and we believe it's very important that

those case reports be scrutinized carefully. And you've heard that we made an attempt to try to do that with an expert panel.

It's not that we're not familiar with these. McNeil submitted more than half of these cases to FDA. So we saw them long before this process went along, and even with our best efforts, such cases often remain sketchy and often have lack of detailed information.

As a result, it's very important that we understand that there are difficulties, extreme difficulties, in determining causal relationships between the fact that acetaminophen as reported in association with an hepatic event, but more importantly, that the cases lacked reliability of dosing information.

And as a result, these cases can be used to indicate that people misuse OTC and prescription products. FDA has said that. We agree with that. They do indicate that people misuse these products, but the data cannot be used to assess the risk of a specific dose level or to use doses to assess special populations as FDA did their analyses. And it is the dosing data that is the basis for much of their assessment.

Now, let's go on. We want to tell you what we think we ought to do. You all know that management of everyday aches and pains is an important consumer benefit. We think that the data continue to say that acetaminophen remains the safest OTC pain reliever when used at recommended doses, and the very things that we talked about suggest that there are not very many potential interactions in spite of all of the theoretical ones postulated.

No substantial evidence to suggest an interaction with anticonvulsants or with Gilbert's disease, and certainly the data don't suggest even with alcohol a need to reduce the dose for consumers of alcohol.

Obviously, consumers deserve the right dose. We spent no time talking about the right doses. We gave you lots of data. The right dose of acetaminophen is 1,000 milligrams four times a day.

What we think is important to this whole process is consumer attitudes and some of the behaviors that we've talked about. And through this process we've gained some insights into consumer medication use behaviors that we think are very important to think about.

And we've already begun the process of

implementing new label changes and initiated education efforts to focus consumers on the proper use of medications.

Consumers need to know product ingredients, and they need to be able to find that information on their package. They need to know proper dosing and proper use of medications. They need to know that they should avoid taking more than the recommended dose of any product, especially acetaminophen, not use two products containing the same ingredients during the same period of time, and recognition that all medications have risks when taken inappropriately or an overdose.

As we've said before, we're committed to try to do the right thing. To this end, we've initiated what we think are some appropriate modifications to the label of our products.

On the front panel, the ingredient names appear more prominently on all of our products than they ever have before, and that is included on the cough-cold combination products. We believe this is important for all products in the category, and we have brought industry support for this.

On the back panel we have already modified the overdose warning to include specific language not

only to react quickly and not wait, which we've done for years, but language that says taking an overdose may cause serious health consequences, and we're stating here today that we will modify it further so that it says taking an overdose may cause liver damage.

We think others in the industry should follow and put similar types of warnings on all of their pain relievers, and as we will demonstrate if you go to the other room, we're committed to a broad range of consumer and health professional education programs.

Now, we wish we --

CHAIRMAN CANTILENA: Excuse me, Dr. Temple. If you can just hold your comments for just a couple of more minutes, please, that will give you five minutes over.

DR. TEMPLE: Okay.

CHAIRMAN CANTILENA: Thanks.

DR. TEMPLE: We thought you might be interested to know that there also are some other ongoing research looking at long term use of acetaminophen because this sometimes comes up. We have two additional ongoing trials looking at long term use, four grams a day, one a placebo controlled

trial of three months' duration and the other an active control trial of 12 months' duration.

There have been previous trials looking at long term use of acetaminophen. We think these will help add to that database.

And now we'll speed through these, but we do have some issues that we wanted to raise. As you've heard, a lot of comments have been made about the AERs data system or case reports in general, and we're concerned whether AERs is an appropriate surveillance system for an old drug with a well known safety profile and whether AERs reported doses are accurate or inaccurate.

If AERs reported doses are inaccurate instead of accurate as you're asked to say, what conclusions can be drawn? And are the assumptions inherent in a system like AERs applicable to acetaminophen, which is most often associated with an intentional overdose when it is designed to work best with drugs that are taken at recommended doses?

We think that we would like to hear from the committee if they have some ideas about ways to do prospective data capture, some type of surveillance system targeted at specific issues, such as the outcome of exposures to OTC pain relievers that might

give us better ideas about the future.

Clinical studies do address specific issues, still have to be done, and can prospective clinical trials -- should prospective clinical trials using large overdoses of acetaminophen be conducted?

In addition to our labeling proposals, you've heard that a large part of the problem involves also prescription combination products or use of prescription products in combination with OTC products, and we're interested in your thoughts on what can be done to improve FDA oversight of prescription consumer labeling.

You'll see we have made a lot of accomplishments we can talk about in the question and answer session.

And lastly, even though FDA didn't mention that most of the medication errors occurred in the under two age group, we're really concerned about what we can do now to establish consensus on pediatric labeling for children under age two.

Thank you.

CHAIRMAN CANTILENA: Okay. Thank you, Dr. Temple and the rest of your team.

We'll actually now hear two five minute presentations from other sponsors, and so then if you

can hold your questions, and we'll have questions at the end of the next session.

The next speaker from Wyeth is Dr. Steven Cooper.

DR. COOPER: Good morning. Yes, I am not Dr. Temple.

My name is Stephen Cooper, and I am the Senior Vice President for Global, Clinical and Medical Affairs at Wyeth Consumer Health Care.

First, let me apologize for being a late entry on the list of speakers, but unforeseen circumstances have made it necessary for me to make this presentation.

At this point, let me emphatically state that all over-the-counter analgesics, including ibuprofen, naproxen sodium, quitoprofen, aspirin, and acetaminophen, meet the criteria set by the FDA for safe over-the-counter use. For all of these over-the-counter drugs, serious adverse events are very rare.

My purpose here today is to clarify some misleading information repeatedly presented by one sponsor in their background package on the increased number of adverse events and deaths if consumers switched form acetaminophen to over-the-counter NSAIDs.

These clarifications are critically important for the public and the committee to hear because of the misleading premise on which the extrapolations of data were based. Unfortunately, the authors of the document chose to blur the issue by using patients taking high dose, chronically administered prescription NSAIDs as the basis for calculating risk.

These patients are more susceptible to adverse events as a result of their underlying diseases. It should be no surprise that under these conditions of high dose NSAID drugs and extended duration of drug use, the extrapolated data favored acetaminophen.

The fair and appropriate comparison would be between OTC dosage regimens of NSAIDs and acetaminophen. This more objective approach comparing apples to apples would show minimal, if any, increased risk in gastrointestinal bleeding from OTC doses of ibuprofen.

Based on my comprehensive review of the data, I would like to make the following observations starting with the acetaminophen issues.

Point one, in overdose situations, acetaminophen can result in serious and irreversible

liver toxicity. In any given year, the number of deaths for acetaminophen reported by the American Association for Poison Control Centers is approximately 20 times that for ibuprofen.

Point two, there are over 400 single entity and combination acetaminophen products in the over-the-counter marketplace in addition to the prescription combination products. Given this, it is not surprising that some consumers unknowingly take multiple products containing acetaminophen, leading to unintentional overdose.

This potentially can put consumers in a life threatening situation due to the delayed onset of clinical symptoms of acetaminophen toxicity.

Point three, acetaminophen is predominantly used in over-the-counter, single entity products and combination products, both over-the-counter and prescription, at its maximum allowable 1,000 milligram dose. Obviously this results in a narrowing of the therapeutic window between the safe and the toxic dose.

This may be justified if the efficacy data support the use of the highest dose. However, there are scant data from well controlled clinical trials to support the use of acetaminophen, 1,000 milligrams, or

for that matter, any dose in over-the-counter combination products.

Point four, in the sponsor's document, they strongly defend the use of 1,000 milligrams because they claim 650 milligrams does not even reach effective plasma levels. Given this, it is a curious contradiction that they also present efficacy data on their newest combination prescription product, which contains 650 milligrams of acetaminophen.

Their own data clearly shows 650 milligrams of acetaminophen is effective.

Point five, another important aspect of the issue being debated today relates to the safety image of acetaminophen that is portrayed in most consumer advertising. The image of a totally safe ingredient may exacerbate excessive use and contribute to the silent danger resulting from overdose.

And now for the NSAID issues.

Point one, for OTC ibuprofen, its regimen is 1,200 milligrams a day versus 24 to 3,200 milligrams a day for prescription use. Unlike acetaminophen, the OTC directions for use clearly specify that the consumer should take one tablet of 200 milligrams and only if necessary, a second tablet may be taken.

In addition, OTC use of NSAIDs is limited to a maximum of ten days, whereas prescription use is chronic.

Point two, and the final point, gastrointestinal bleeding from NSAIDs is a real phenomenon, but there is no question that it is dose related, and OTC regimens of ibuprofen have a very low relative risk approaching one.

This is because of the low dose, short term use and wide margin between the OTC and prescription dose. Independent investigators, like Dr. Michael Langdon (phonetic) and David Henry, have documented the low relative risk of ibuprofen.

In fact, Dr. Langdon has stated that for gastrointestinal bleeding, the incremental number of deaths above the background rate due to low dose ibuprofen is very low and may be nil.

In conclusion, the inference made in the background material that if acetaminophen users switch to OTC NSAIDs there would be many more deaths is completely erroneous and unsubstantiated. OTC ibuprofen is as safe as acetaminophen when used as directed, and in overdose situations, unlike acetaminophen, ibuprofen rarely is life threatening.

Thank you for your time and your

consideration.

CHAIRMAN CANTILENA: Okay. Thank you, Dr. Cooper.

The next speaker from Bayer is Dr. Heller, and the FDA has allocated one, zero minutes, ten minutes for Dr. Heller.

DR. HELLER: Thank you.

So you now have the real Dr. Heller.

(Laughter.)

DR. HELLER: Mr. Chairman, members of the committee, officers of FDA, I'm Allen Heller, Vice President of Global R&D of Bayer Consumer Care. I appreciate the opportunity and Bayer appreciates the opportunity to address the committee and to be here today in these proceedings which we believe can only benefit the consumer.

As you may know, Bayer is a leader in the field of analgesics, in the development and marketing of analgesics, and has 100 years' experience in this area. While we are perhaps best known for Bayer aspirin, we also have in our portfolio a variety of products and some products that contain acetaminophen. Examples are Alka-Seltzer Plus for cold-cough-allergy symptoms, Midol for menstrual symptoms.

Importantly, we do not market any single

ingredient acetaminophen product. Also, we do not market any pediatric analgesic product.

All of our acetaminophen containing products are combination products. These products offer the consumer meaningful benefit by providing multi-symptom relief and the convenient dosing.

Our experience is consistent with the spontaneous reports as reviewed by FDA in indicating that our acetaminophen OTC combination products are not associated with significant adverse events, including liver failure, and we'll go into that in a bit more detail.

Nevertheless, Bayer has made voluntary changes in its labeling consistent with recommendations from the CHPA in order to better educate the consumer about the potential risk of simultaneous use of multiple products containing acetaminophen, which has been alluded to.

In thinking of your deliberations today, Bayer values the importance of clear, concise, and ingredient specific labeling. We support and we have adopted and we have implemented the labeling proposed by the Consumer Health Care Product Association regarding the risk of use of multiple products containing acetaminophen, and based on our experience

and the experience with respect to FDA's record of spontaneous reports, we submit that additional regulatory intervention beyond appropriate labeling on OTC combination products is probably not warranted.

Just reviewing the FDA database very briefly, this experience suggests a low hepatic risk potential for combination products which amounted to only 12 percent of the cases overall, but we do recognize, and it has been mentioned, that spontaneous reports have limitations in their interpretation.

Also keeping that in mind, we have received at Bayer no reports of adverse hepatic events, whether serious or non-serious, and in terms of overall -- for our combination products -- and in terms of overall adverse events for our OTC -- our only acetaminophen combination products, you can see that adverse events of all types, and this is over a six year period, are relatively rare, as are serious adverse events, which constituted only one percent of those adverse events that have been reported to us.

We think that we know the reason for this apparently favorable safety profile for combination products. This relates to the use pattern of these products. These products are typically used for a short period. They are used for well defined self-

limiting symptoms, and these combination products contain other active ingredients which because of their effects tend to limit dose.

We believe that these factors enhance the benefit-risk relationship relatively for these combination products.

We further believe that the enhanced warning that we have adopted and already implemented will further educate consumers regarding the potential risk, simultaneous risk of multiple products containing acetaminophen.

Regarding labeling and considerations of labeling actions, labeling should be based on substantial evidence. Individual ingredients should be labeled and regulated based on their unique pharmacology.

We also believe that labeled and used appropriately, that all of the OTC analgesic ingredients are safe.

A few more before I go to the conclusions. A couple more comments on labeling.

Labeling decisions should be based on appropriate risk assessments that make fair comparisons across equivalent dose paradigms and indications.

There have been public discussions of estimates of the public health effects relating to hypothetical switching scenarios. We have seen -- and the committee has seen in its briefing materials -- estimates related to hypothetical switching scenarios that are incorrectly based on data from prescription use that are not relevant to OTC use.

We would caution the committee to view these hypothetical scenarios with skepticism, these hypothetical switching scenarios. In fact, there are recent findings that demonstrate that there's comparable GI risk across all of the OTC analgesics when they're properly compared, and we will present and discuss those data tomorrow.

Moving quickly to my conclusions, Bayer concurs with the FDA that all OTC analgesic ingredients are safe and effective. Regulatory action with acetaminophen should be independent of other ingredients and should be based on sound, scientific principles.

The proposed labeling on simultaneous use of acetaminophen containing products, the strengthened warning we believe is appropriate, and we submit that further interventions for acetaminophen containing OTC combination products are probably not warranted.

I thank you all for your attention, and once again express Bayer's appreciation for participating in this process, which we believe can only benefit the American consumer.

Thank you.

CHAIRMAN CANTILENA: Thank you, Dr. Heller.

We have actually one additional speaker for this portion of the program, a late entry into the agenda, Dr. John Dent from GlaxoSmithKline. Five minutes for Dr. Dent.

DR. DENT: Thank you very much, Mr. Chairman. I promise I won't take more than two.

I'm John Dent, Senior Vice President, Consumer Health Care at GlaxoSmithKline.

GlaxoSmithKline is the second largest consumer health care company in the world and part of the second largest pharmaceutical company in the world. We're global manufacturers and marketers of products containing aspirin, ibuprofen, and acetaminophen, or as it's called in Europe, paracetamol.

These ingredients, when used as recommended, have for decades relieved pain and fever in hundreds of millions of people safely and

effectively. As with any medicine, if the directions for use are not followed, there is a risk of adverse events, and in extremely rare circumstances with each of the ingredients, adverse events do occur.

However rare these events are, it is incumbent on the agency and the industry, working with health care professionals, to insure the U.S. consumer understands how to take these medicines safely. We believe this can be achieved through labeling, enhanced consumer and health care professional education.

Insuring that consumers continue to have direct access to these important medicines at effective doses will safeguard against massively overburdening the emergency and primary health care system.

As the FDA have stated, these medicines are effective when used as directed at the doses approved. The challenge is to insure everyone understands how to use these important medicines safely.

Thank you very much.

CHAIRMAN CANTILENA: Okay. Thank you. Thank you very much.

We'll now have the opportunity to ask

questions of the panel to all of the speakers, and what I'd like you to do is to signal. I owe Dr. Brass a question from the earlier session. So we'll start with Dr. Brass, and then I'll be looking for hands.

DR. BRASS: Thank you.

As I reflect on this issue, it seems to me that the data from the epidemiologic studies and the information from the databases are actually consistent with a number of hypotheses and inconsistent with very few.

So I would like to take a giant step backwards and again start with Dr. Temple's conclusion that hepatotoxicity results when doses of acetaminophen exceed a threshold amount, and I would like to pose a hypothetical question to him and other members of his team.

Specifically if -- and I emphasize the "if" -- there was a population whose glutathione stores were substantially lower than the average population, would not that population have a substantially lower threshold for the dose that would induce hepatotoxicity?

DR. TEMPLE: Well, the answer is if that were theoretically the case -- can we turn that off so we -- yeah. I'll try to find the right function. Got

it. Thank you.

But you know what? I think it would be helpful for Dr. Slattery to talk a little bit about this issue of glutathione source because it's a hypothetical issue, and the clinical data don't --

DR. BRASS: I didn't ask for clinical data. I asked at this point, given the absence of data, to help us think about the problem. If there was such a population identified by any means, would it be at increased risk?

DR. TEMPLE: Yes. I haven't seen a population, such a population.

DR. BRASS: And similarly, a population or individuals with substantially increased 2E1 activity for any reason would similarly be at risk.

DR. TEMPLE: But the alcohol data --

DR. BRASS: I didn't say anything about alcohol.

DR. TEMPLE: -- shows that there is increase, but it's a very small amount.

DR. BRASS: Well, okay. Again, I want to start with the principles because then if we agree that those concepts have validity --

DR. TEMPLE: I'm not sure they do. You said substantial increased risk.

DR. BRASS: Okay. Well, that's why if you don't think they're legitimate, then tell me why they're not legitimate.

DR. TEMPLE: Okay. The data on alcohol. Come on up here, John.

(Laughter.)

DR. TEMPLE: The data on alcohol demonstrate that with alcohol induction you get a small amount, not a substantial amount, of 2E1 induction.

DR. BRASS: Okay. Again, my question didn't include alcohol, and that there was no control -- no measurement of actually the degree of 2E1 induction in those experiments, and we saw only mean data. So we didn't know if there were individuals that had larger increases.

So my background question remains if there were individuals as I described, would they be at increased risk?

DR. SLATTERY: You wouldn't be disappointed if I was a little bit less argumentative.

(Laughter.)

DR. SLATTERY: And that is that there are lots of studies in animals, right? And we know that if we treat animals with butionine, sulfoxamine,

diethylmaleate, we substantially deplete glutathione, and this has to go down very low to where you're at 25 percent of total, you know, hepatocellular stores that you start to see toxicity due to NAPQI.

I think when you try to translate some of this into the human population, one of the things really is to, you know, think about the safety margin and whether or not, you know, when you're talking about a one gram dose four times a day, whether or not populations that people point to, you know, those that have not eaten for some period that might be fasting or something are actually kind of safely covered by that current dosage recommendation.

And my gestalt is really -- and I can't site data -- you know, from just kind of what we know about the incidence of acetaminophen poisoning, is that the current recommended dose is safe even in those populations.

And I would make the same sort of comment about 2E1 induction.

DR. BRASS: Yeah, okay. I'm comfortable with that because I think the bottom line is a challenge to those who hypothesize risk --

DR. SLATTERY: Yes.

DR. BRASS: -- to present data that there

are populations with the characteristics that I describe.

DR. SLATTERY: Yes.

DR. BRASS: So that, for example, if there was a population of chronic alcohol abusers, a subset of that population that had substantial glutathione depletion for some reason, that might be of concern to us.

DR. SLATTERY: Yeah. If I could comment on, you know, alcoholics and alcohol abusers for just a moment, I have been puzzling over this for 20 years, and I presented some of our data here, and one of the things that I always come back on this is the NIAAA Web page will state that there are 18 million alcoholics and chronic abusers of alcohol in the United States, and I've seen data produced by McNeil that says 23 percent of the U.S. adult population has used acetaminophen in the last week.

And if we put those numbers together, there are four million people who have been exposed to the combination, and I really have to ask the question as to whether or not if you identify a chronic abuser of alcohol, you know, as a person at risk whether or not that risk category has really been adequately and specifically identified.

And those numbers to me, which I think are very simplistic, say no. I feel a little bit like Richard Feinman, you know, taking the ring and the ice water and kind of smashing it on the desk, but I do think there's some evidence that we should look at there.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Johnson next.

DR. JOHNSON: I have a question that I think is again for Dr. Slattery and really on related lines. Dick Winchelbaum at Mayo has done a fair amount of work in recent years on genetic variability in the sulfur transferases, and you talked a little bit about genetic impact relative to the glucuronadation pathway. I'm wondering if you can comment on the impact of genetic polymorphisms in the sulfur transferases or the glutathione transferase.

DR. SLATTERY: Yeah, I'm sorry, but I haven't seen any specific data on that with regards to acetaminophen disposition. He's actually used different model compounds.

You have to remember that the sulfation pathway is about, you know, half as important as the glucuronide pathway, and I think that's a very good question, but I just don't have data to answer you

with.

DR. JOHNSON: And I don't know the specifics off the top of my head of the sulfur transferase polymorphisms. My recollection is it's not absent enzyme or nonfunctional enzyme, but --

DR. SLATTERY: Yes, it's diminished activity. It's diminished activity, and I actually think it has more to do with the promoter than the coding region. So it's not like a SIP 2D6 sort of polymorphism or something like that.

So, yeah, it addresses the issue of underlying variability.

If I can continue for one more second, it raises another question. In the morning session there was a bit -- well, there was a statement that the variability and kind of the formation of NAPQI across the population might be as great as 60-fold, and I really do doubt that assertion. I've done a lot of work with a drug called Busulfan and used in marrow transplantation that really can be viewed as a direct probe of the GST A11, which is the GST that makes this conjugate in the glutathione pathway.

And these are, you know, patients that are in reasonably good shape as they come in for transplantation. Coefficient of variation and the

clearance of that compound is only about 16 percent. That goes across data that was analyzed when we had 300 patients. We have 1,300 now, and it seems to be about the same.

But I didn't mean to digress from your question on PST.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Crawford.

DR. CRAWFORD: Thank you, Mr. Chairman.

This question is directed to Dr. Bowen and Dr. Temple.

I appreciated the summaries of the selected toxicology studies on acetaminophen use, but I note a void of applied research data that considers the social, behavioral and cultural factors in risk assessment of possible acetaminophen induced hepatotoxicity.

I did hear as you described how your company has initiated labeling changes and educational programs. As we consider potential recommendations for risk assessment and management, I ask if you have any data available on variables such as what Dr. Day mentioned earlier, consumer comprehension of labeling and information, safety impact of different packaging, the effectiveness of those different educational

programs.

And, Dr. Bowen, you had mentioned the widespread use of acetaminophen in diverse populations and different cross-cultural populations. I ask also do you have any data on outcomes and socio-cultural subpopulations which could be used to determine potential higher risk.

DR. BOWEN: Gee, yes. Some. We do.

(Laughter.)

DR. BOWEN: Sheryl Hanks, who works for us at McNeil, Sheryl, do you want to just talk to that?

MS. JENKINS: Sure. Thank you.

We have several surveys available to us. We're fortunate to have Dr. Kaufman here from the Sloan Epidemiology Unit at Boston University that's helped to inform us.

In addition, we have several other survey studies that have informed us. They include the Medascope survey, NICBI (phonetic) survey, and then an internal survey done conducted by McNeil that provides some more in depth.

If you take them all together, we get a story, and it's a very interesting one. We bandied about the 23 percent use of acetaminophen in the past week. The vast majority of consumers appear to take

their medications, all OTC analgesics, within recommended dose.

We find that there's approximately one percent or less that exceed doses during either -- one percent or less during the past week. Some consumers may report more having ever exceeded those doses, and then these surveys also inform us about why that might be the case.

And I know that FDA has also had some suppositions about why that may happen.

There are some respondents who report not being aware of the active ingredient in their medication, and that ranges depending on -- and this is in single ingredient -- that depends on what the product is and what the active ingredient is.

And so it can range from about ten percent who are aware to about 50 percent who are aware of the active ingredient. So it would appear that more information could be given depending on what the information that we have from these respondents and how generalizable that really is.

Respondents in many of the surveys also report why they are exceeding these doses, and I'll just rank them because it's very difficult. There are different population sizes, but I can rank them.

In many cases they want faster relief. So they exceed the recommended dose.

They have severe pain, and that will inspire them to exceed the recommended dose.

They feel that they're not getting -- they feel that OTC analgesics may be weaker and, therefore, they're inspired to increase the dose, or they've taken an Rx version of the medication previously.

DR. CRAWFORD: Excuse me.

MS. JENKINS: Yes.

DR. CRAWFORD: You've answered my question in terms of some survey data. Have you tried any other assessment or evaluation methods to look at some of these social behavioral factors?

MS. JENKINS: By manipulating and actually conducting interventions?

DR. CRAWFORD: Yes.

MS. JENKINS: No.

DR. CRAWFORD: Thank you.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Laine.

DR. LAINE: I had a couple of questions for Dr. Dart.

First related to the -- while he gets up there -- the panel review of experts. I guess if I

were doing a study like that, first of all, I assume that they were all paid by McNeil, but if I were doing a study like that, I'd probably want them not to know that McNeil was sponsoring this review. I'd probably not want them to know the issues, i.e., that there was an FDA hearing that was going to evaluate hepatotoxicity of acetaminophen, issues such as that, and another issue probably is what I would do is probably mix in cases other than just the FDA reports or else they'd know that every single case was an FDA report.

I was wondering if those conditions, any of those conditions were met in your review. That's my first question.

DR. DART: It sounds like most of those are actually to the company and not to me. Among the things that --

DR. LAINE: I thought you were chair, but I'm sorry.

DR. DART: Well, I said that it was funded by McNeil. So --

DR. LAINE: No, but do they know that it was funded by McNeil? Do they know that the issue related to an upcoming --

DR. DART: Yes, of course they knew.

DR. LAINE: Okay.

DR. DART: There were cases mixed in to see whether or not there was a lot of variability in how they rated things.

DR. LAINE: So other than the 300 cases, there were other fake cases and things mixed in.

DR. DART: That's right.

DR. LAINE: So they did not know how many of those were there.

DR. DART: That's right. There was another --

DR. LAINE: Do you know how many? Were there a lot of them? I'm just meaning were there a lot to them?

DR. DART: There were about 15 or 20, as I recall.

DR. LAINE: Out of 300 and --

DR. DART: Out of 281, I think it is.

DR. LAINE: But they did know the issues as well, why --

DR. DART: They did know that --

DR. LAINE: So, again, I'm not saying that these people aren't extremely bright and, you know, noble, but obviously their potential --

DR. DART: Well, we were very up front

about that, and as I said in my presentation, I can say that the discussion was spirited, to put it mildly, and especially from the different backgrounds that people came from.

DR. LAINE: And that's my second question. I was interest in your comment that people under report suicide intention. Do you have data where that is?

My anecdotal view from a large medical service at a large urban hospital is exactly the opposite, and there are kind of both medical and legal problems with doing that as well. So I'm surprised that, you know, residents are counseled not to do that.

So I was just wondering are there data to actually show that those are or is that just an anecdotal view?

DR. DART: It's a widespread anecdotal view. I've been in three different programs, and that was the consistent teaching, and it's logical. I mean, why would you put something in a binding record that could prevent the patient from having insurance coverage, for example, in the future?

And it is a recent development. I'll freely grant that that's probably within the last five

to ten years that that has evolved.

DR. LAINE: I understand, but I actually don't see it at our hospital. I mean, one of the reasons you would do it is because the patient goes out and kills himself. There are certain medical legal responsibilities to you out in the future.

DR. DART: Well, the point is to record what happened, not to put pejorative comments in there. So they would say if the patient said, "I took ten grams," yes, they would write down, "Patient took 20 tablets," or whatever it was. They just wouldn't label it as suicidal.

DR. LAINE: I don't think we should let that go unchallenged. I mean, we certainly teach our residents that what should go into the medical record is the truth, and I think most other centers do that.

It's extraordinarily important that the next physician reading that record knows what the truth, what the honest opinion of the loss and record it in the record and thought.

And the idea that we would be falsifying the record or giving the impression that it's widespread in this country that we falsify medical records, I think is utterly wrong, and I think that should be corrected before it becomes widely --

DR. DART: Okay. Well, I think you're misstating what I said.

CHAIRMAN CANTILENA: Hold on just a second, please. If we can get off the subject of that, I happen to -- you know, like I'm on your side, but that's the same thing in our institution as well. It should be, you know, the truth that's in there, but let's not spend any time on that.

We have four more individuals who will ask questions, and for a program that we will actually extend the questions until 12:15, and then we'll have the full hour for lunch.

So if you don't mind, just excuse me so that we can get back on track and perhaps over lunch we can all chat about that issue. But, Dr. Cohen, you're next.

DR. COHEN: Yes. Given that we're, I guess, mainly concerned about the unintentional overdoses at this meeting and later on today we intend to work on some risk management strategies, I guess I'm kind of left disappointed that there isn't more information about the causality, and we haven't really discussed that very much at all.

In my own work, we handle a lot of anecdotal reports with mostly our reports that come

through the medication AERs reporting program, and we've seen a number of contributing factors that have been reported to us mostly by health care professionals, misunderstanding the way that the concentration is expressed on the label, for example; the brand name extensions, where one brand of drug really has multiple ingredients, when people think they're taking other than what's actually in that package.

And maybe we can talk about some of these others a little bit later, but I can tell you that when we receive these reports, we follow up. We ask how did this happen, either through the health professional, who then could contact the patient if necessary, and it doesn't seem like that's being done here, and I don't understand.

I mean, there's thousands of these reports that have occurred over the years. Isn't there that basic root cause information that we need to -- you know, with our decision making this afternoon, I think we were starting to hear some of that with Dr. Crawford's question. The response was excellent, and it was cut off.

Is there more information? What is causing these events to actually occur? That's what

we need to know. I wanted to hear about that.

CHAIRMAN CANTILENA: So are you asking that to Dr. Temple?

DR. COHEN: To the company, to any of the -- even FDA.

CHAIRMAN CANTILENA: Okay. Well, how about if we just ask the company at this point? And this afternoon we'll have an opportunity to ask others.

Dr. Temple, would you like to address that issue?

DR. TEMPLE: Let me just comment. This is really a question of adverse event reporting since most of the data sets are adverse event reports. And generally speaking, much of that data is extracted from things like medical literature, other sources, and so you're limited in terms of what's available to you.

That's why we are suggesting that we need a more prospective, proactive approach to getting at the root of this problem, because that -- it's only through that route that you can really get to the next level of why consumers behave the way they do.

DR. COHEN: Because right now I think we're mainly being asked to speculate about the

changes that are needed in order to reduce these unintentional events. And I wish there was more information out there.

I know that you do as well.

DR. TEMPLE: Yeah.

DR. COHEN: But without that information, it's hard to make the changes that are necessary with the labeling other than speculating what might work. So we'll probably be doing that this afternoon.

CHAIRMAN CANTILENA: Well, that's one possibility.

Okay. Dr. Elashoff.

DR. ELASHOFF: Yes. This set of questions and comments applies to the talks by Dr. Slattery, Dr. Dart, and Dr. Koff.

On none of the reports of the individual studies either in tabular or in graphical form was it identified whether those plus or minuses were standard deviations or standard errors. I'm assuming they're standard errors. Some of them are really quite large.

On some of the slides there was no indication of what the sample size was. When it was there, they were mostly quite small.

It was implied that if the means were similar or the result was not significantly different,

then an important difference could be ruled out. With this kind of sample size, I don't think that's true. I think we ought to see for all of those a 95 percent confidence interval so that we could tell what differences the results are actually consistent with.

DR. SLATTERY: If I can respond to at least my part of that, in my case there were standard deviations. The n's were small. These were small, you know, studies done simply in my laboratory with regards to the effect of rifampin or omeprazole. I'd love to see those done in larger patient groups.

It's kind of the standard size, you know, group size that you see in simple drug interactions, studies of that kind. I don't know if there are other specific data that you'd like me to speak to.

DR. ELASHOFF: Well, both the talks by Dr. Dart and Dr. Koff had similar issues, and if a study is small, it still should be demonstrated that it's big enough to have the power it needs to have to detect what might be important.

DR. SLATTERY: Yes. These were not powered as pivotal studies, but they were prospective. If you take a look at other evidence in the literature, for example, anticonvulsants and their effects on NAPQI production measured the way that we

did, you'll find an agreement on that.

Lloyd Prescott has published the same sort of thing. So I am, you know, rather confident in that and would welcome, you know, a larger study, and the same with regards to 1A2. I think we'd confirm the result.

DR. DART: In the studies that I presented, there were two, I think. The repeated supertherapeutic ingestion did have 95 percent confidence intervals on it. We can go back and see that if you want. That was a total of 270 patients or so, and the largest group had about 140 and the smaller ones had 40.

In the alcohol study, that was actually -- we've done two studies on that for a total of 260 patients, half of which, roughly half of which are acetaminophen and half that didn't, and that had a power to detect a difference in the AST of just 13 units. So I didn't put that on there.

DR. KOFF: In the study that I showed of the single dose, that was standard errors. In the Benson study done, again, in 1983 and in the Dargere study, standard deviations were shown.

And, again, these were obviously studies done several years ago before epidemiologic importance

of powering studies was done, and these were -- that's the data we have.

DR. ELASHOFF: That's why it's advantageous to do confidence intervals, so that you can actually see what the study does show.

DR. KOFF: Yeah. Well, we're waiting for the Dargere paper to be published in full. It's still just an abstract that appeared in Hepatology. The Benson paper, of course, did not have adequate data for me to go back and do confidence limits. Maybe we can -- Gordon is here -- we can get some of that old data and see if we can get those numbers.

CHAIRMAN CANTILENA: Great. Thank you.

Dr. Davidoff, then Cryer, then Williams, and then lunch.

DR. DAVIDOFF: I had a question I guess primarily for Dr. Bowen but for others. It regards language because the term "rare" or "very rare" has been used, and I certainly wouldn't disagree that in terms of a denominator of hundreds of millions of doses, some of the events we're talking about can be seen as rare.

But that's looking at rates essentially. But if you start looking at the absolute numbers, I really question the use of language like "rare" and

"very rare."

According to the test data submitted by Proctor & Gamble, in a three year period there were 316,000 cases of reports of acetaminophen analgesic single medication incidence of which roughly 128,000 were considered to be intentional, but 178,000 considered unintentional.

How reliable that is we are not certain. Anyhow, the bottom of those, there were about 1,800 serious and of those 768 were serious or major.

So I really wonder. I mean, if we saw those numbers in connection with other kinds of etiologies or context, I'm not sure that we would be using the terms "rare" and "very rare."

As a final sort of comment related to that, the analysis of the AERs data which suggested that only about a quarter of them, namely, about 75 out of the total cases were, in fact, definite or probable acetaminophen related. We also know that the reporting to that database is only of the order of between one and ten percent.

So if you multiply out, you're now talking about something in the range of 750 to 7,500 cases over whatever period the AERs has been conducted. Again, I would suggest that that's consistent with the

serious toxicity or death in the range of about 1,000 in three years. So I really wonder whether we're talking about rare events or not.

DR. TEMPLE: Let me just comment first on the poison center, the test data, because there is important data if you're going to talk about this during the day.

Having been involved in establishing that system, the accidental cases in this case are largely young children getting into product that they're not exposed to. So you can't use the same ratios about unintentional. So they're largely accidental ingestions in kids.

And, secondly, poison centers report exposures which simply means somebody took a product and they called a poison center to know what to do about it. So they can't give you any perspective on the size of the serious problem.

So we tried to focus on serious cases that might cause harm. That's maybe how we got from the bigger numbers down to the things that are really, really relevant.

DR. BOWE: I think that's right, and perhaps the word "rare" should have been "very uncommon" or "uncommon" if that's more comfortable for

you. Because I think that rare has a definition and a regulatory one from the point of view of looking at the number of cases in any given database.

I would like to comment, however, that some of the cases that were in the adult AERs system, although they were collected over three years, actually occurred over a 25-year period. So that should be also in your calculation.

CHAIRMAN CANTILENA: Thank you.

Dr. Cryer.

DR. CRYER: I just wanted to follow up on Dr. Brass' earlier question about data from clinical experiences from in vivo studies about the effects of glutathione depletion, and this is specifically for Dr. Dart.

I would just wonder whether or not your data set on alcohol users who were given acetaminophen also just asked a subpopulation of patients who were fasted. And if so, what were your observations in the fasted subpopulation?

DR. DART: Yeah, we did determine body mass index on all of the subjects, and so we looked at it from various different ways because if you look in the literature, there's not one number that's used to represent malnutrition or under nutrition. For

example, some will say 21. Some will say 20. So we did it both with 21 and 20, and there's basically a third and a fifth of the patients that fell under those two categories.

Now, this is a post hoc analysis, but if you take those two groups and compare the means of that way, then again you find no difference between them and anyone else in the study.

DR. CRYER: Were all patients fed?

DR. DART: The patients could eat after they were in the institution, right.

CHAIRMAN CANTILENA: Okay, and our final question from Dr. James Williams.

DR. WILLIAMS: My question has already been addressed.

CHAIRMAN CANTILENA: Okay. Very good. All right. What we'd like to do now is break for lunch for one full hour. We will meet back according to my watch about 12:15 -- 1:15.

Thank you.

(Whereupon, at 12:17 p.m., the meeting was recessed for lunch, to reconvene at 1:15 p.m., the same day.)

1

2

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

(1:24 a.m.)

CHAIRMAN CANTILENA: We'll go ahead and begin the second portion of our open public hearing. The first speaker, Dr. Sarah Erush, has been granted ten minutes, ten minutes by the Food and Drug Administration.

Dr. Erush.

DR. ERUSH: Thank you.

I'd like to present to you today a review of acetaminophen overdoses admitted to our hospital with an emphasis on the unintentional cases to demonstrate that these patients actually exhibit greater morbidity and mortality than do the intentional cases and, as such, suggest that further measures be put in place to prevent these tragedies from occurring.

My name is Sarah Erush, and I'm the Director of the Drug Information Service at the hospital of the University of Pennsylvania in Philadelphia. HUP is a 700 bed tertiary academic medical facility with Level 1 trauma and transplant services. It serves the tri-state region of Pennsylvania, New Jersey, and Delaware, and averages about 35,000 admissions per year.

Of note, none of these are pediatric admissions. So all of the data I'm going to present to you today is in adult patients.

Our adverse drug event program is run by Dr. Karen Shalaby and operated by our Drug Information Service. It averages 600 reports per year and obtains them through both spontaneous and targeted reporting methods.

Prior to 1998, we like many other institutions did not routinely report acetaminophen overdoses because we did not feel that they were preventable adverse drug reactions. Due to Dr. Shalaby's prompting, in 1998 we did begin to routinely report all acetaminophen overdoses, and much to our surprise, we found a significant number of unintentional overdoses which we feel are in all likelihood completely preventable.

Therefore, we undertook a review of all the cases that we had in our database for the past four years and found 54 reports of acetaminophen overdose, and of the 47 cases that we've been able to review to date, 23 of those, or a full 50 percent, were unintentional overdoses.

To demonstrate our certainty that these patients are actually unintentional, of the 23

patients identified, in 13 of those cases the attending physician was so certain that the patient had mistakenly overdosed on the drug no psychiatric consult was requested.

In ten cases where a psychiatric consult was requested, in all cases psychiatry stated that these patients had no intent to harm themselves.

In looking at the patient demographics between the two groups, you'll not that the patients in the unintentional group are slightly older than the intentional group, that there's an even split between male and female patients, with more female patients in both groups, and that the intentional group was more likely to be directly admitted to the hospital while the unintentional group was more likely to be transferred in.

In looking at where we could accurately determine the amount of acetaminophen ingested, it was very interesting to note in the unintentional group that the median and average doses were between six and eight grams per day, which while above the recommended maximum of four grams per day, is still far below the ten to 15 gram dosage usually considered to be toxic.

In determining whether the patient obtained the drug either through prescription means or

over the counter, again, it was evenly split between both groups, but it was interesting to note that in the unintentional group more patients took single entity acetaminophen products than did combination products, making it clear that they knew that what they were taking contained acetaminophen.

The reasons for the ingestion in the intentional group are listed here with pain, toothache, insomnia and headache being the most common reasons.

The primary reason for exceeding the maximum dose was a frustration with unrelieved pain, with many patients stating they knew they were exceeding the recommended dose and did so because they thought it was such a safe drug.

We define an acute exposure as any exposure that occurred in less than seven days, and as expected, in the intentional group most of these patients were a one time overdose situation, but the unintentional group, you'll note, often took their drug over a period of one to three days and, in fact, 30 percent of these patients took the drug over a period of greater than seven days.

Therefore, as expected, when looking at the average peak acetaminophen levels in this group,

the unintentional group has a much lower peak acetaminophen level than does the intentional group. But unexpectedly, when looking at the average peak levels of ALT, AST, INR, and total bilirubin to indicate their liver function, the unintentional group had significantly higher levels than did the intentional group, indicating that this group had experienced significantly greater toxicity than did the unintentionals.

In terms of length of hospital stay, the patients in the unintentional group also stayed longer in terms of both ICU days and total days of hospital stay, again, indicating that they had greater morbidity than did the intentional patients.

And most distressingly, in terms of patient outcome, in the unintentional group more patients did not have resolution of their liver disease. More patients were evaluated for transplant. More patients were transplanted, and more patients died as a result of their unintentional overdoses.

We were so intrigued by the unintentional group exhibiting such greater morbidity, considering they had taken lower doses and taken them over an extended period of time, that we undertook a review of risk factors to see if we could find any differences

between the groups, and in fact, we looked at hepatic disease, alcohol use, drug abuse, and concomitant disease.

And as you'll note, we didn't find great differences between the groups with the possible exception of more alcohol use in the unintentional group.

And when we further reviewed this risk factor, we found that the primary difference lies where the unintentional patients maybe had more patients who had chronic alcohol abuse with an acute ingestion on top of that.

However, it was interesting when we looked at the number of risk factors per patient. A full 96 percent, or 22 of the 23 patients in the unintentional group, had at least one of the previously defined risk factors for acetaminophen hepatotoxicity, and that was compared to only 70 percent in the intentional group.

And as these curves demonstrate, the unintentional group was more likely to have one or more risk factors than did the intentional group, leading us to believe that the existence of risk factors does have an impact on toxicity in unintentional ingestions.

So I'd like to summarize the data that

I've presented to you in stating that in the 47 patients that we looked at, unintentional overdoses accounted for a full 50 percent of those cases; that the doses in these patients were lower and ingested over a period of one to three days; that the unintentional cases had greater toxicity when judged by LFTs, INR, and length of stay; that the unintentional cases also had higher transplant and death rates than did the intentional group.

Additionally, the influence of risk factors remains present, but unclear, though alcohol use and having more than one risk factor was more prevalent in the unintentional group.

We also wanted to point out to you that the hospital costs for the unintentional group were nearly double of that of the intentional group, and that's interesting to note because if you'll remember they didn't have double the length of stay. So, again, these costs are indicative of the severity of illness of this group.

And if we take these numbers and we extrapolate this cost data to similar institutions around the country, the cost of acetaminophen overdoses in general to the health care industry easily runs into the hundreds of millions of dollars.

We also wanted to note that the results that we're presenting to you now are very similar to those that have been published previously, which indicates to us that this is a significant ongoing issue in the United States that, again, we would like to propose is preventable.

There are multiple recommendations that could be made or considered at least to prevent this tragedy. Obviously, we don't advocate taking acetaminophen off the market. However, we do think that educational practices for both health care practitioners and consumers alike could be significantly improved.

Of major importance would be to continue to encourage the reporting of acetaminophen overdoses. As we mentioned before, most institutions do not report these overdoses because they do not feel they're preventable adverse drug events.

And notably, none of the cases that we presented to you today were reported to our local poison center, which is where much of the data on unintentional overdoses comes from, and much of that poison center data on an unintentional overdoses is accidental ingestions in children, while all of the data that we've presented to you today is in adults.

As such, we'd like to propose that this problem is potentially severely underestimated, and further data is better needed to define the risk for the unintentional patient population and to target educational practices for them.

We also need to erase the notion with both prescribers and patients alike that acetaminophen is such a safe drug.

Changes in labeling, packaging, and even perhaps the addition of small amounts of antidote to acetaminophen products are all other things that could be considered to help improve the safety of this product.

And finally, I'd like to close with a quote from one patient that was representative of many that we found in our chart review and clearly demonstrates patients' ignorance of the potential dangers of this drug.

"If I'd known it would make me this sick, I never would have taken it."

We respectfully ask the committee to consider taking measures to improve the safety of acetaminophen products and thereby the safety of the American public.

And we thank you very much for allowing us

the time to present this today.

CHAIRMAN CANTILENA: Thank you very much.

Our next speaker in the public hearing is Susan Winckler, American Pharmaceutical Association.

MS. WINCKLER: Thank you for the opportunity to present the views of the American Pharmaceutical Association, the national professional society of pharmacists.

I am Susan Winckler, a pharmacist and an attorney and APHA's Vice President of Policy and Communications.

My comments today will focus on the pharmacist's perspective on the use of acetaminophen, possible sources of problems seen with the OTC analgesics, and the need for consumer education.

In the interest of full disclosure, APHA frequently partners with federal agencies, consumer groups, the pharmaceutical industry and others to develop educational tools for pharmacists and consumers. The association did not receive funding to participate in today's meeting, and the views I am presenting are solely those of the association and its members.

APHA's 50,000 members include pharmacists, practitioners, pharmaceutical scientists, student

pharmacists, and pharmacy technicians. These members provide care in all practice settings, such as community pharmacies, hospitals, and long-term care facilities.

In those settings we help consumers manage and improve their medication use, including the appropriate selection and monitoring of prescription and OTC products, such as acetaminophen.

Acetaminophen is widely used in both prescription and OTC analgesics and cold, allergy, and sinus preparations. Pharmacists, other health care providers, and patients frequently select acetaminophen products because of the excellent safety profile and relatively low number of side effects and for its appropriateness in special populations, such as pediatric patients and patients with asthma, hypertension, or gastrointestinal disorders.

It is of significant therapeutic value for millions of patients. However, acetaminophen, like all other drug products, is only safe and effective when it's used appropriately.

Improving the public health and safety with respect to medication use is the pharmacist's and APHA's highest priority. APHA supports the review of adverse events to determine if a medication's benefits

are outweighed by its risks.

While reports of adverse events are possible indicators of problems, many of these reports may be incomplete and do not show causality. It is hard to determine if acetaminophen was the sole or primary cause of the reported events, what other factors may have played a role, or if the use of acetaminophen before the adverse event was only a coincidence.

We know, however, that patients may unintentionally exceed the recommended dosage by taking the incorrect dose of the medication or ingesting multiple products that contain acetaminophen. This can occur when caregivers for pediatric patients accidentally give the wrong dosage because they use an inaccurate measuring device; incorrectly determine the dose based on the child's age rather than the child's weight or are not aware of the difference between products, such as acetaminophen suspension and concentrated drops.

In other cases, patients with multiple symptoms unknowingly ingest multiple products that contain acetaminophen. For example, a patient on the prescription drug percocet for significant pain may also take nonprescription Sudafed severe cold formula

to treat cold symptoms, unaware that both products contain acetaminophen.

In other instances, patients exceed the appropriate dose by taking more than the recommended initial dose, taking another dose before the appropriate time interval has passed, or exceeding the maximum number of doses in a day because they believe it will increase the medication's effectiveness.

While all of these situations can result in an overdose of the medication and enlarged doses may contribute to an adverse event, these examples are a sign of incorrect usage by the consumer that may well be due to not reading or reading but not following the label directions.

To combat this problem, we must work with consumers to become educated about the importance of both reading and following label directions for both prescription and OTC medications. The widespread use of OTC analgesics may have led consumers to become complacent about their use.

A study by the National Council on Patient Information and Education, NCPIE, found that while 95 percent of consumers read product labeling when selecting and using an OTC medication, they often don't read the entire label and instead select the

information they view as important.

And what consumers may view as important doesn't necessarily match with what health care providers and regulators view as important. As an example, only 34 percent read the information about the active ingredient, and only 21 percent of those consumers read the warnings information.

Consumers must be reminded that any medication, including OTCs, has the potential to harm if it's used incorrectly. A survey of caregivers underscored this point as only 28 percent of them were aware that OTCs could have side effects, and only 36 percent could name a possible side effect that could occur for a given medication.

Consumers must be encouraged to read product labeling, to take the medication as directed, to learn of possible side effects, and understand what to avoid while taking the medication.

Consumers with questions or special needs should also be encouraged to talk to their pharmacist or physician before taking any new medication or combining multiple products.

APHA recommends that all prescription and OTC products containing acetaminophen be clearly marked. Patients often identify with the brand name

of the medication they are taking, but are not aware of the product's active ingredients.

For example, patients may report that they are using the product Tylenol, but a survey found that only eight percent of those individuals could also report using acetaminophen.

OTC products should contain verbiage, such as "contains acetaminophen," on the product's front panel, preferably in combination with the drug name.

Additionally, acetaminophen containing prescription drug products could be identified through the use of auxiliary labels placed on the prescription vial by the pharmacist, and both products should include warnings about therapeutic duplication.

We're pleased that Bayer, McNeil, and other manufacturers of OTC products have announced revision of labeling for their acetaminophen containing products to emphasize the active ingredient and include an overdose warning.

APHA encourages the FDA to recognize the industry's efforts in this area and to further advance their efforts by allowing important dosing information for patients under the age of two to be added to the product label. The inclusion of this dosing information may prevent overdoses caused by inaccurate

dose estimates.

In conclusion, acetaminophen is one of the safest and most effective OTC and prescription drug products available for pain relief when it's used correctly. It is important that the agency does not reduce access to this valuable pain medication.

The agency should work with product manufacturers, pharmacists, physicians, and consumer groups to educate consumers on the appropriate selection and use of all OTC products, including acetaminophen, aspirin, and other NSAIDs.

Consumer education activities, such as NCPIE's Be Med Wise public education campaign, is a great way to educate consumers about the need to both read and follow label directions and to ask their pharmacists if they have any questions.

Helping consumers learn how to appropriately select and use OTC medications is key to reducing product overdoses and related adverse events.

Thank you for your consideration of the view of the nation's pharmacists.

CHAIRMAN CANTILENA: Thank you.

Our next speaker, Mr. Ray Bullman from the National Council on Patient Information and Education.

MR. BULLMAN: On behalf of the National

Council on Patient Information and Education, I am pleased to address the FDA's Nonprescription Drugs Advisory Committee.

Found in 1982, NCPIE, as we call ourselves, is a nonprofit coalition of 135 member organization, including national consumer and patient organizations, health care professional associations, voluntary health associations, manufacturers, and government agencies.

The FDA is represented on an NCPIE board of directors in a nonvoting liaison capacity.

In the interest of disclosure, neither NCPIE nor I received funding to participate in today's meeting. Support for the Be Med Wise campaign, which I'll describe, was developed by NCPIE, and provide an unrestricted educational grant from McNeil Consumer and Specialty Pharmaceuticals, and subsequent Proctor & Gamble.

The appropriate use of medicines, specifically the exchange of useful information between consumers and health care professionals to foster such appropriate use, has been at the heart of NCPIE's mission for 20 years. Our national education campaigns have featured themes such as "Team Up and Talk," "Have Your Medicines Had a Checkup," and

"Educate Before You Medicate."

While my comments may not necessarily reflect the opinions of each NCPIE member, there's universal support among our membership for the vital role that high quality health care provider and patient communication, public awareness and education play in promoting safe and appropriate use of medications.

Whether consumers are self-medicating or have a new prescription, we urge them to ask questions, to share information about other medicines they're taking, and to report any problems to their health care professionals.

Today this is more important than ever before, with nonprescription medicines accounting for six of the top ten medicines taken by Americans according to the Sloan survey published in JAMA on January 16th of this year.

Also in January of this year, NCPIE launched our Be Med Wise public education campaign to promote the wise use of nonprescription medicines and to raise awareness about the new Drug Facts label on over-the-counter products.

Survey research commissioned by NCPIE last year indicated that many consumers do not recognize

the potential for harm if they take more than the recommended dose of an OTC medicine, take more than one OTC product containing the same active ingredient, inappropriately combined OTC and prescription medicines, or inappropriately combine medications and dietary supplements in some cases.

As specifically relates to OTC pain relievers, our poll found that only 34 percent of respondents taking an OTC medicine for headache could correctly identify its active ingredient. Two thirds, 66 percent, either incorrectly identified the active ingredient or did not know what the active ingredient was.

We also found that one third of respondents report having taken more than the recommended dose of an over-the-counter medicine.

Our campaign activities to date have included extensive use of television, radio, print, and the Internet to encourage consumers to be med. wise when selecting and using over-the-counter medicines. Message points that relate specifically to the committee's deliberations today include over-the-counter medicines are serious medicines that can cause harm if taken incorrectly.

Many over-the-counter medicines contain

the same active ingredient. So make sure you know the active ingredient or ingredients in each of the medicines you plan to use or to administer to others.

Compare the active ingredients if you're taking multiple medicines.

Always read the OTC drug label carefully and follow dosage instructions, warnings, et cetera.

Tell your doctor and pharmacist the names of all the medicines you are taking, particularly before a new prescription is introduced to the regime or a new OTC is introduced.

When in doubt about choosing and using an over-the-counter medicine, consult your doctor or pharmacist.

Our campaign Web site, bemedwise.org, highlights the fact that many OTC medicines contain the same active ingredient and includes a graphic demonstrating the number of products, both prescription and OTC that contain acetaminophen, ibuprofen, aspirin, and naproxen sodium.

In August, NCPIE conducted a five-city media tour coinciding with the back-to-school season to convey ten tips to parents and caregivers when giving over-the-counter medicines to children. Working with our network of pharmacists and pharmacy

organizations, NCPIE will next develop and disseminate Be Med Wise messages to consumers at community based pharmacies across the country.

An initial product will be a series of brochures and Web based messages with the working title of which will be promoting the wise use of over-the-counter pain relievers, followed by similar titles addressing the most widely used categories of OTC products.

I've summarized the work of our Be Med Wise campaign because I feel there are some insights that may prove helpful in the context of today's meeting. As specifically relates to the Advisory Committee, NCPIE recommends that FDA sustain its support for consumer and patient education by continuing its collaboration with organizations like NCPIE and other organizations.

Continue to develop and disseminate consumer directed messages about the Drug Facts label as an educational resource, calling special attention to knowing the active ingredient in your medicines and comparing products when taking multiple medicines.

Regularly assessing or supporting research on consumers' understanding and use of the Drug Facts label. Such consumer research can help guide

collaborative efforts to inform and educate about appropriate use of medicines.

And finally, to commit support and resources for an ongoing national consumer medicine safety and education partnership, such an effort could be modeled after the multi-stakeholder partnership for food safety education with its highly visible fight BAC food safety campaign. That's B-A-C, in which FDA is intricately involved. It could incorporate timely and relevant messages about, for example, risk recognition and management and medication error reduction.

NCPIE first proposed such a sustaining medication, education, and safety campaign to the FDA in 1998. Broad goals for such a campaign would be to educate consumers and health care professionals about changes and improvements in medicine education, to promote question asking, information seeking and information sharing as valuable tools to improve communication and knowledge, and to better equip consumers and caregivers to recognize and/or act on medication related errors or problems.

NCPIE envisions the Be Med Wise campaign as a multi-year effort to support and enhance consumer's informed self-care decision making when

selecting and using over-the-counter medicines. As such, it could serve as the foundation for a broadened, multi-stakeholder, collaborative national consumer medicine education and safety partnership.

Throughout our history, the FDA has worked closely with us on many educational campaigns. Our partnership to promote the Be Med Wise messages and especially the new Drug Facts label has been rewarding.

We commend NDAC for highlighting important safety issues and the role that consumer education can play as we continue working together to insure the public's wise use of medicines.

Thank you.

CHAIRMAN CANTILENA: Thank you, Mr. Bullman.

Our next speaker is Ms. Kate.

MS. KATE: I'd like to thank you very much for allowing me to be here today.

On April 18th, 1995, my son Marcus said to me, "Oh, Ma, I think I'm going to die."

I told him I would never let that happen. I had no idea at that time how serious his medical condition was or that it would continue to get worse. A few weeks before, our son had injured his wrist.

He had a severe sprain and was prescribed acetaminophen with codeine by our family physicians. He took the medication for the prescribed time.

When the prescription was finished, he continued to have some pain and purchased an over-the-counter acetaminophen product. During this time, we spoke to Marcus frequently. These calls were to check on how he was doing, and I would always ask the usual Mommy questions.

How's your wrist? How do you feel? Are you eating?

He said his wrist didn't hurt as much, but he wasn't feeling well and wasn't very hungry. When we spoke to him on the Friday before Easter, Marcus said he thought he was getting the flu. He said he was nauseous, had body aches, and a temperature.

We found out later that these are also symptoms of acetaminophen toxicity.

At this point he purchased an over-the-counter flu remedy, also containing acetaminophen. On Easter Sunday he felt bad enough to go to a local hospital. After being in the first hospital for two days, Marcus was transferred to another hospital and put on the organ donor list.

On April 24th, eight days after entering

the hospital, and with no donor liver available, we stood next to our 23 year old son's hospital bed and watch and listened as he slowly slipped from our lives.

I and my husband and our other two sons watched as the color drained from Marcus' face when his heart stopped. Our previously healthy, happy son was gone.

When we found out that the cause of death was liver failure due to acetaminophen toxicity, we didn't know what to think. Our search for an answer started. We found out that acetaminophen was a leading cause of drug overdose and death in the United States and the United Kingdom. We learned that the numbers of deaths per year were in the hundreds and that adverse events were over 100,000 per year.

We also found out that fasting was as much a factor as alcohol when combined with acetaminophen to cause liver failure.

If our son or my husband I had had even an inkling that acetaminophen toxicity existed, I feel that the outcome of our story would be totally different, perhaps no story to tell at all.

My husband and I have made contact with other families across the country who have had family

members die to acetaminophen toxicity. They thought they were alone.

This panel knows the statistics. You know they're not alone. To this day we meet people, tell them our story, and we still get the same response: I didn't know that.

We continue to meet doctors who are not aware of the frequency of acetaminophen toxicity. My husband has educated our local EMS to the signs of toxicity. Most people know about stomach problems and bleeding associated with NSAIDs. Why aren't they aware of acetaminophen liver problems?

We've taken on the project of trying to educate as many people as we can, but it should be the responsibility of the manufacturers to educate consumers. With yearly profits in the billions from acetaminophen products alone, I feel that the funds are available for consumer education.

Commercials for prescription drugs warn of possible side effects and to consult your physician. You have the guidance of your doctor. With over-the-counter products, you're on your own. If companies are permitted to advertise their products, they should be require to inform people that fasting, alcohol, preexisting liver problems can lead to liver damage,

liver failure, and death.

There's a phrase that makes me sick. The phrase is "risk-benefit ratio." It seems that it's acceptable that a number of people will die if you sell a certain amount of medication. It's not acceptable. There's no acceptable ratio when one of those people is your loved one, and important information was withheld, information that has been known for 20 years.

I know this panel will do what's right. You have to. You can't allow more innocent men, women, and children to suffer from the adverse effects cause by acetaminophen.

Seven years have passed since Marcus' death. Don't let another year pass and more families go through the unbelievable pain and sorrow that our family has had to endure. Sometime positive has to result from such an unnecessary death as our son's.

In his memory we have given out seven scholarships in his name to his high school. Another tribute would be to stop the additional suffering due to the greed and indifference to consumers by manufacturers of acetaminophen products.

This is Marcus when he was three. It's one of our favorite pictures. That's Marcus on his

aunt's boat up in Maine. Marcus just enjoying himself with his friends. This is Marcus' graduation picture.

And as requested by some of the people I have been in contact with, two families requested me to show pictures. This is Wendy. She died at 28 from acetaminophen toxicity. And this is Cindy, dressed in a gown to go to her class reunion two months before she passed away.

And I just hope by looking at these faces that you know and hope you know that death is not an acceptable side effect.

Thank you very much.

CHAIRMAN CANTILENA: Okay. Thank you very much.

Our next speaker is Dr. Caroline Riely.

DR. RIELY: Good afternoon. Thank you for the opportunity to provide testimony here.

My name is Dr. Caroline Riely. I'm a professor of medicine and pediatrics at the University of Tennessee at Memphis.

I'm providing testimony today on behalf of the American Liver Foundation, the leading national voluntary health agency dedicated to the prevention, treatment, and cure of hepatitis and other liver diseases through research, education, and advocacy.

We are here today because we are concerned about the issue of adverse reactions in the liver to over-the-counter medications.

As a hepatologist caring for patients with both acute and chronic liver disease, I suggest both acetaminophen and nonsteroidal anti-inflammatory drugs, such as ibuprofen, to my patients depending on the setting.

For example, acetaminophen is the antipyretic and analgesic of choice for patients with chronic, non-alcohol related liver disease, despite its well known association with hepatotoxicity.

Acetaminophen, normally a very safe drug, is an hepatotoxin under certain conditions, and we've heard a lot about that today. The therapeutic window for this agent is quite narrow. The usual adult dose is one gram by mouth every four hours, but a single dose of 20 grams can cause lethal hepatotoxicity.

Many believe that four grams per day is a safe level, but some have suggested that it may be more prudent to use two grams a day as the maximum safe dose for those who regularly use alcohol.

Acetaminophen is a constituent of many combination medications, both over the counter and prescribed. So a patient may take two forms of

acetaminophen without being aware of that fact.

For example, a patient may use Tylenol P.M. and percocet and may inadvertently exceed the safe dose.

This is particularly a problem in the pediatric population. Well meaning parents administer multiple doses, can reach toxic dose inadvertently resulting in liver injury. In this age group, the problem is magnified by the multiple formulations available. The parent may not be aware that the preparation advised for infants, a concentrated form given in drops, is much more potent than the syrup administered by teaspoon in older children. Toddlers using the infant formula but given by the spoonful may inadvertently develop injury to the liver.

We're concerned that the present marketing practices make it very difficult to find the standard dose formulation, the 325 milligram pills. As a result, the consumer thinks that the extra strength preparation is the only one available.

Given the narrow therapeutic window, this failure to market the lower dose may contribute to increased adverse events.

At the American Liver Foundation, we would like to encourage an active approach to this problem

and would like to participate in any way that we can. There needs to be greater awareness on the part of all, the consumer or their parents, the pharmacist, and the physician.

We would advocate an innovative educational effort to help minimize these problems. For example, the package warning in use now are too small, difficult to reach, and thus may appear to the consumer to be unimportant.

An educational effort at the site of purchase would be useful. There could be signs or brochures in Spanish as well as English available at the display shelf or at the checkout counter. Pharmacists distributing acetaminophen containing prescription drugs, such as percocet or vicodan, should label the bottle to indicate that the medication contains acetaminophen, with a warning that toxic doses may be obtained if the patient is an alcohol user or taking OTC acetaminophen.

Public service announcements on TV would be helpful, and the manufacturer should promote the use of the 325 milligram tablets or at least give them equal shelf space with some informative guidelines as to which dose is appropriate for whom.

Likewise physician education is important.

Physicians need to know all of the medications, both over the counter and prescribed, that their patients are taking. They should be aware of the narrow therapeutic window for acetaminophen and its interaction with alcohol. And pediatricians and family practitioners should go over with the parents the appropriate dosing for the various pediatric formulations.

We realize that the discussion of the NSAIDs is tomorrow's topic. We would like to take this opportunity to remind the panel that NSAIDs, such as ibuprofen, are potentially toxic in patients with chronic liver disease, leading to renal failure at even modest doses.

Thus, in this setting acetaminophen is a better choice for the treatment of pain or fever.

Acetaminophen is a good drug, proven so over decades. Efforts at education of the consumer and the professional will result in an even better safety record for this agent.

The American Liver Foundation wishes to thank the FDA for convening this panel. We believe that these drugs represent only the tip of the iceberg. We need a better understanding of the potential for hepatotoxicity of all therapeutic

agents.

Thus, we recommend the creation of a task force to examine the issue of drug induced hepatotoxicity. We need better review mechanisms and studies to address this problem. The American Liver Foundation stands ready to assist in this initiative.

Thank you very much for allowing me this opportunity to share our views with you today.

CHAIRMAN CANTILENA: Thank you, Dr. Riely.

Our next speaker is Dr. Peter Lurie.

DR. LURIE: Good afternoon. I'm Peter Lurie, a physical with Public Citizens Health Research Group in Washington, and I have no conflicts to disclose. We take no money from government or industry.

Let's start with some history. In 1977, a review panel not dissimilar to the present one recommended the following warning for acetaminophen containing products: "do not exceed recommended dosage because severe liver damage may occur." And a second piece of advice: "do not exceed recommended dosage or take for more than ten days because severe liver damage may occur."

The FDA chose to ignore this advice. Now, a quarter of a century later, we're looking at what is

literally an epidemic of fatal acetaminophen associated poisonings, a near doubling just between 1995 and 1999, and estimates -- we've heard data just recently suggesting it might, in fact, be an under estimate of 458 deaths per year according to death certificate data.

Acetaminophen is the leading cause of toxic drug ingestion in the United States.

The FDA has estimated that at least 57 to 74 percent of ingestions are intentional. Yet the issue before the committee is described as, quote, unintentional acetaminophen hepatotoxicity, which is an illogical restriction of this debate and seemingly a capitulation to the idea that nothing can be done for those making suicide attempts.

In fact, many suicide attempts are impulsive and are, in fact, cries for help. And many of them will turn out to be fatal despite that. Most, however, are not fatal, and fatality rates are related to the doses consumed.

I think writing off what is, in fact, the leading cause of death related to acetaminophen overdose makes absolutely no sense to me, and I'm going to suggest a number of things that might be done that will not only have an impact upon the intentional

overdoses, but will also have a ripple effect upon unintentional ones.

Now, one of the things that some countries have done, something not mentioned at all in the FDA briefing packet for reasons unclear to me, is that numerous countries have, in fact, tried to do something about this problem. The most recent of these occurred in the United Kingdom where in September of 1998, there was a restriction placed on the number of acetaminophen packs, acetaminophen tablets per pack: 16 if you purchased the drug in a supermarket, 32 if you bought it from the pharmacy, with an overall restriction on 100 tablets that could be bought. Otherwise you had to go and get a prescription from your doctor.

Early evaluations of the program showed decreases in total and severe acetaminophen overdoses, as well as decreases in acetaminophen overdose related liver transplant and death.

All of this, it seems to me, should be informative to the committee and are the kinds of things that should be considered.

I'm going to go through a six point plan of things that could be done, and let me start with the first, which is consumer access to risk

information. We heard a lot about that. In fact, most of what the committee has heard so far has been about access to information as a consumer group.

Of course, we're in favor of that, but we'd like to see it go well beyond that.

On the matter of risk information though, what we have is woefully inadequate. Obviously it's not even consistent with what the review panel recommended a quarter of a century ago.

In addition, there should be a general warning about liver toxicity. The label should mention the symptoms of liver toxicity and advise patients to at least consult their medical care providers if they start to develop any of those symptoms.

It should also warn against the simultaneous use of multiple acetaminophen containing products, and there should be a warning on the box the way it was done with aspirin and Reye's Syndrome, and there has been an enormous impact on Reye's Syndrome deaths as a result of that box warning.

We also support a patient information leaflet in each packet. Advertising, although not regulated by the FDA, the FTC could require the kinds of warnings that we see on direct to consumer

advertising for prescription products at this point, and they could talk about the dangers of overdose, and so on.

I would also like to see the FDA writing articles in medical and lay journals and running late night or any time PSAs regarding the dangers of acetaminophen overdose. So that's number one.

But what can be done beyond the customary claims to education and the need to do all of this when, in fact, very little will, in fact, be done?

We can reduce the maximum daily doses, and that would be a good place to start. Among unintentional adult acetaminophen related liver toxicity cases reported to the FDA or published in the medical literature, the median daily dose was five grams a day. Now, the total maximum dose is set by FDA to be four grams a day. So that itself is a very small margin for error.

Of course, for certain groups of people the medium maximum dose among -- sorry -- the median daily dose among those with hepatotoxicity was still lower: for alcohol users, 4.6 grams per day; for liver disease patients, four grams a day, literally the maximum dose; hepatotoxicity, patients taking other hepatotoxic meds., 3.9 grams per day.

The margin of safety for those with those underlying conditions of particular drug use is clearly too small. There needs to be a reduction in the maximum daily dose for them, but given that overall the total daily dose was five grams a day, only 20 percent higher than what the FDA says is safe as a maximum, we think you should consider lowering the maximum dose for everybody.

Point three, reduce the per tablet doses. Because there is a practical limit on how many pills a suicidal patient can take, it's only logical that reducing the strength of the individual dosage forms to 325 milligrams per tablet would yield important benefits.

It's also likely to benefit pediatric patients who get into the medicine cabinet and ingest acetaminophen containing products, as well as those who are unknowingly taking multiple acetaminophen containing products.

Four, standardize the liquid formulations. The FDA reports 25 cases of pediatric hepatotoxicity. In at least four of them, teaspoonfuls of medication were administered instead of dropper fulls. I mean, I remember as a physician being very confused about that when patients make the transition, you know, to

toddlerhood. And obviously patients are just as confused.

While acetaminophen suspension has 32 milligrams per mL, the drop contain three times as much, which is obviously ample opportunity for overdose.

All liquid forms of the drug should be required to have the same concentration. That would really address that problem in a straightforward and simple fashion.

Remove irrational acetaminophen containing combinations from the market. Forty-nine percent of over-the-counter acetaminophen sales is in the form of combination products, but most, if not all, of these combinations are just irrational. Patients and their parents should be encouraged to use only the medication that they need, not lapse into this shotgun approach to drug therapy.

The use of combination products with elaborate and often misleading brand names discourages patients from learning the generic names of active ingredients, potentially leading to overdoses when taken with other acetaminophen containing drugs. Approximately 25 percent of patients with liver toxicity collected by the FDA had taken more than one

acetaminophen containing product.

Finally, more research. We've heard some mention earlier of the idea of combining acetaminophen containing products with N-acetylcysteine, a drug that is used to treat acetaminophen overdose. We are not aware of data that show that that's an efficacious approach, but certainly it does merit further study.

Now, none of these approaches, the six things that I have mentioned will be enough on its own to eliminate the problem of acetaminophen overdoses. Multiple approaches clearly are necessary here, not one simply restricted to labeling and advertising, but beyond that. If not, we'll be looking back a quarter century from now and somebody else will be able to look back and say, "This is what the FDA panel was told or what the FDA panel reviewed, but nothing was done," and we'll have more cases on our hands.

Thank you.

CHAIRMAN CANTILENA: Thank you, Dr. Lurie.

Our last speaker for this section is Dr. Lou Lasagna from Tufts University.

Dr. Lasagna.

DR. LASAGNA: Thank you.

My name is Lou Lasagna. I am Dean Emeritus of the Sackler School for graduate biomedical

studies at Tufts University, and for many years I was Director of the Center for the Study of Drug Development, first with the University of Rochester and then at Tufts.

My interest in analgesics harks back to a half century ago when I became involved in clinical trial design and the search for nonaddictive substitutes for morphone and for new pain relievers that would offer safer and more effective analgesia.

I am here today to present my personal views. I have not received compensation for my time, although I must say I've had many satisfying collaborations with industry, with pharmaceutical companies over the years. And some of the research at our center is supported to this day by unrestricted grants from industry.

My goal today is not to propose solutions to the complicated questions before this committee, but rather to raise some issues that I believe need to be part of your deliberations.

The remarks that I am going to make can be applied to any of the drugs under discussion during this two-day meeting. Three issues of special concern.

First, dose response versus benefit to

risk. OTC drugs, as you know, are by their nature expected to be generally safe in recommended dosages and regimens. Intuitively the minimal effective dose should be utilized in an OTC setting.

Even with generally safe drugs, excessive amounts of drug or dosages above the ceiling dose for efficacy can increase the risk of toxicity. The balance of benefit to risk of all OTC drugs is related to the dose response for efficacy.

In the ideal world, the ceiling dose for efficacy is well below the toxic levels allowing a wide therapeutic window. I think the committee needs to determine for both single entity and combination products whether the current dosages and regimens are, in fact, optimal based on the available data.

Two, combination policy. A second point relates to the way OTC combination products are approved for marketing. Under the FDA guidelines for analgesics, for example, a combination policy clearly states that the contribution of each ingredient must be shown in well controlled clinical trials. This policy is applied to all new combination drugs that seek approval under NDAs.

In contrast, under the monograph system, the monographs for analgesics and for cough, cold,

allergy products allow combinations to be marketed based on historical data of the individual components. There are often few data from controlled trials to justify the dosage of the analgesic ingredient or even to indicate whether the ingredient contributes meaningfully to the overall efficacy of the combination.

This policy has led to proliferation of a vast array of cough, cold, allergy products that contain an analgesic. Both acetaminophen and aspirin at their highest allowable doses are often part of these combination products.

For newer analgesic drugs, the problem would appear to be under greater FDA control because of their NDA status requiring clinical studies to demonstrate both efficacy and safety.

Well, what is the optimal dose of analgesic that should be in OTC combination products? Whenever possible, data from well controlled clinical trials should drive this decision making process.

Third, promotion of products. Although there is fierce competition among pharmaceutical companies, they all have a responsibility as they would admit to be honest with the consumer. This honesty needs to be reflected not only in the product

label, but in promotion material in print, in TV, and so forth.

OTC drugs, like all other drugs, are neither perfectly safe nor free of drug interactions. You may remember that two to four percent of all the new drugs approved by FDA are ultimately removed from the market, usually because of serious toxicity rarely occurring that was not detected prior to marketing.

This message, I would submit, needs to be clearly articulated to the consumer. Overstating the safety image of any drug can lead to adverse effects. Well, the big question in closing is I would submit the following. Are there ways by labeling changes, by educational material for parents, consumers, patients, for physicians, other ways which without loss of therapeutic benefit can make what are generally safe OTC products even safer.

I don't have the answer, but I would submit that the question is one that deserves an answer.

Thank you.

CHAIRMAN CANTILENA: Thank you, Dr. Lasagna.

What I've actually done, I've asked the FDA to help to focus the committee somewhat by

reviewing if they would, you know, the regulations that cover, you know, the labeling for the over-the-counter drugs, and I think there's someone prepared with a couple of slides that they can sort of get us all on the same page.

And then I've also asked Dr. Ganley if he could scan in some images of labels from some of the over-the-counter drugs that we've been talking about just so you have an idea of, you know, what they look like, you know, as they're out there today.

So if you don't mind start with that.

Okay. Sandy just reminded me that that panel also has a handout that was just given out just as we came back from lunch that has a lot of this information and some sample labels as well.

While that's coming up, Dr. Ganley, perhaps you could, you know, remind the committee in terms of jurisdiction over advertising for the over-the-counter drugs, if you can just sort of clarify that because a lot of the comments we've heard have touched on the advertising and marketing.

DR. GANLEY: Yeah, for OTC drugs, the FDA has jurisdiction over the promotional labeling, which would be the label on the package, package insert.

If there's a stand within a store, that's

sort of considered promotional labeling. What we wouldn't necessarily regulate, which is regulated by FTC, would be TV advertising, magazine advertising, newspaper advertising and things such as that.

CHAIRMAN CANTILENA: Okay. Thank you.

MS. LUMPKINS: Okay. You all are well aware of the Drug Facts format. The Drug Facts format is FDA's effort to simplify the labeling for consumers, to put information in discrete places consistently across all labels.

So basically this is one of the regulations, and this is the outline format that Drug Facts labeling should take. So this was our first attempt.

Now, there are some other regulations that regulate the labeling of these products. One of these deal with the PDP that's also pertinent to this discussion today. Those are the statement of identity regs.

And what I'm going to do is I'm just going to briefly describe for you what the statement of identity needs to be. The statement of identity basically has two parts. It's the established name of the drug, and the established name of the drug is usually the name that's in the compendial like the

USP.

Beyond that, there is the pharmacologic category of the drug. That's its general purpose, its, you know, analgesic antipyretic kind of a thing.

In combination products, the statement of identity gets to be a little bit problematic. The regs. allow for if there is no established name of the combination, say, acetaminophen pseudoephedrine tablets. The manufacturer has the option of using the general pharmacologic category. This is pertinent to today's discussion because that means for those combination products, the active ingredient is not going to appear on the PDP.

And what we've done is we've scanned in some of the principal display panels of some of the commonly marketed over-the-counter drugs containing acetaminophen both in combinations and single ingredients so you could sort of see.

There's also another aspect to the statement of identity that you should be aware of. The statement of identity is required to be printed in a size reasonably related to the most prominent display of the trade name. It's also required to be in direct conjunction with the trade name.

Now, this works very well when you're

dealing with a single entity ingredient where they're required to have something like acetaminophen on the front panel.

For the combination products, that gets to be a little bit more problematic because you're dealing with, you know, cough-cold product or nasal decongestant, antitussive. So you're not going to get that visual message to consumers that this product may have acetaminophen in it.

Sir?

DR. GANLEY: I just want to clarify when you're saying PDP you're saying principal display panel.

MS. LUMPKINS: Right. Sorry about that.

Basically the PDP is described as like the panel presented for display for sale. So that would be the thing that the consumer would see first when they look at the products when they sit on the shelf.

Yes. So basically what you have is flu would be the trade name. We've obviously for obvious reasons blocked out most of the name. This is what you generally see on cough-cold products. This is the general pharmacologic category.

I just have --

DR. GANLEY: Debbie, could you just read

some of those things under there because it's hard to see it back here, too?

MS. LUMPKINS: Okay. The general pharmacologic category for this product is pain reliever, fever reducer, nasal decongestant, cough suppressant.

Nowhere on there is an active ingredient. Totally required by the regulation.

Next one.

This is a generic product that was bought at a local Target store, and it has a little different approach. No problem with the statement of identity there in recognizing that product.

(Laughter.)

MS. LUMPKINS: Again, this one does actually have all of the active ingredients on it. I'm not even sure if I can read them. This is your point of reference here.

Let me see. Push this? Thank you. I never worked one before.

These right here are your active ingredients. This is your trade name. These are your pharmacologic categories.

CHAIRMAN CANTILENA: Okay. And the regulation then just really requires the categories.

MS. LUMPKINS: For combinations that's all that would be --

CHAIRMAN CANTILENA: And not the active ingredients.

MS. LUMPKINS: -- required, yes.

CHAIRMAN CANTILENA: Okay.

DR. GANLEY: I think the other thing is that the regulation isn't really clear on the type size. It says it should be reasonable, and we're always struggling on the NDA side for people to increase the size because that's what they really want to downsize, is the statement of identity or the name of the active ingredient.

And you can see it on that last one where you could hardly, you know --

MS. LUMPKINS: You could hardly read it.

DR. GANLEY: Right. You could show them where the type size in there -- I don't want to pick on that product individually, but --

MS. LUMPKINS: There are others.

DR. GANLEY: -- they're not unique in that regard.

MS. LUMPKINS: Go ahead.

This one, there's your pharmacologic category. This is also a combination.

Reasonably related to the most prominent -- it's a very tricky legal definition. Some people could say, "Well, if you can read it, that's good enough." Other people would say, "Well, it needs to be bigger."

CHAIRMAN CANTILENA: So then in that case, then the active ingredients are on the other side of the box. They're on the back.

MS. LUMPKINS: Right. They would be in the Drug Facts usually for an combination. As you saw, there were some that did try to do both, but you know, you can understand the logistics of the combination, too, because when you've got five and six different ingredients, it gets hard to get all of that and still have all of your trade dress.

CHAIRMAN CANTILENA: Okay. Very good. Does anyone on the panel have any questions for FDA on this point specifically, on the labeling?

Dr. Wood, then Dr. --

DR. WOOD: Is there a fundamental legal reason why the size of the labeling can't be defined? I mean if that was one of the recommendations that this panel was to make --

MS. LUMPKINS: It would require amendment of the regulation, but it's certainly something that

could be done.

DR. WOOD: But there's no reason why this panel couldn't make such a recommendation; is that right?

And similarly, going back to the point that's been made many times today, that individuals overdose on these products because they don't recognize that they're taking the same product in different ways, there's no reason why we shouldn't highlight one of the ingredients to be called out like acetaminophen, for example?

MS. LUMPKINS: Well, you know, the Drug Facts labeling has very specific font size requirements for all of the headings for the minimum font size that's acceptable for the text.

DR. WOOD: Yeah, but that's not what is redone at --

MS. LUMPKINS: Something comparable could be done for statement of identity.

DR. WOOD: Okay.

MS. LUMPKINS: And it's certainly within the purview of this panel to make that recommendation.

DR. WOOD: Okay. Thank you.

CHAIRMAN CANTILENA: Dr. Neill.

DR. NEILL: When people go into the

drugstore or to the grocery store and they look on the shelf, I am used to food labels now telling me a serving size and commonly a grocery store putting a unit price in a common denominator format so that when I'm comparing one bread to another bread, I know the cost per pound.

For medications, because of the way that they are marketed, they may be present in 24 caplet size, 12 caplet, a blister pack, many different formats, and I have no idea whether this panel can make recommendations about how to present cost data or dosage data in addition to that principal ingredient.

If no other recommendation were made, I guess I had not understood, despite being on this committee off and on for the last few years, that the ingredient name was distinct from the category name, and that the category pain reliever-fever reducer was required and the ingredient not.

MS. LUMPKINS: Only in combos. With a single ingredient product, it would be required to state acetaminophen on the principal display panel. So it's just for the combinations where it gets to be a little difficult.

DR. NEILL: But while I could understand the educational value of having the class data there,

for consumers who are attempting to get what they can get for a certain dollar amount and recognizing that combinations in my anecdotal, nonscientific survey make up the majority of that shelf space, and acknowledging that that shelf space is very expensive for products you put up there, I would think that it would be useful to have that there.

And so it is helpful for me to get guidance from staff about, you know, gee, what is within the purview. The information about the regulations is helpful.

CHAIRMAN CANTILENA: Any further questions for the FDA?

I'm sorry. Dr. Cush.

DR. CUSH: Can someone at the FDA tell me why they have oversight on matters of display, but yet have no oversight on the far more influential and pervasive practice of direct to consumer advertising print and media?

CHAIRMAN CANTILENA: Dr. Ganley, do you want to handle that one?

MS. LUMPKINS: Yeah, go ahead.

(Laughter.)

MS. LUMPKINS: I don't have an answer for that one.

DR. GANLEY: Someone from industry could probably answer it better. I really don't know why that distinction.

DR. CUSH: You can't answer the question?

DR. GANLEY: Well, I don't know the history.

DR. CUSH: -- the rule.

DR. GANLEY: Well, we don't set the rules necessarily. Congress sets the rules on us and we write the regulations based on those laws, and so it must be within laws of who provides the oversight for the advertising.

I don't know the historical background related to that, but we can't just go out and write a regulation that's not within the purview of what the law allows us to do, and so I'm assuming that that authority has been given to FTC.

The promotional labeling, a display in the store that has the name of a product on it is still really pretty much labeling until you leave that store, I think. I didn't write it. I just have to follow it.

CHAIRMAN CANTILENA: Just to follow up on that, obviously our panel is advisory to the FDA. Is there a similar panel or some mechanism for feedback

for the FTC, Part 1?

Part 2 is: can the panel recommend items that are sort of under their jurisdiction? And is there any, you know, formal exchange that that would actually get back to them from FDA?

DR. BULL: I would mention that we do have ongoing dialogue with FTC and could certainly explore what the options would be in terms of building more substance into the interaction, as well as the level of oversight, and to take these concerns to them.

CHAIRMAN CANTILENA: Yes, Dr. Clapp.

DR. CLAPP: I'd like to know about the package itself. Once the package is gone, on the medicine bottle is there the requirement that the category name be on the bottle as well in the front of the label?

And if so, is this just for combinations or, I mean, is this just for single ingredient items?

Because my concern is everyone tosses this, and if you have the Tylenol bottle or Tylenol cold and flu and you're depending to read the microscopic vision for those of us who are graduated to the presbyopic types, I'm sure that it's a great challenge to read it on the back of the label, but perhaps on the front, that would be a more reasonable

likelihood that we could read the ingredient.

MS. LUMPKINS: Basically Drug Facts is required on the outer carton. The principal display regulations speak to the outer container, but in reality what manufacturers usually do is their PDP is pretty much displayed on their inner container.

I mean absent, you know, some of the extra things that you might get on a carton, but there aren't any real regulations because the PDP is about the outermost container.

Now, if it's marketed without an outer container, then your PDP becomes the bottle itself.

So sorry.

DR. CLAPP: Is it within the purview of this committee then to make a recommendation that the container itself have an identification of the active ingredient on the outside of the label?

MS. LUMPKINS: I would think it would be.

CHAIRMAN CANTILENA: I'm sorry. Could you use the microphone, please?

DR. GILBERTSON: The immediate container has to have the name of the active ingredient, and it has to have the name of the product, on the immediate container and on the principal display panel.

The other information she's talking about

that's found on the Drug Facts is not necessarily required on the immediate container, but it must have that plus the name of the manufacturer, the number of capsules or tablets. And so there are certain things that are required, especially the name and the active ingredient.

Combinations are different, as she points out.

DR. CLAPP: My question is for the front and the back of the label as being different. When you have a bottle of Tylenol, the front of the label has pretty much the same information as the front of the package, and then as I recall the back has the dosages and --

DR. GILBERTSON: That's not in the new Drug Facts format you're looking at, I presume.

DR. CLAPP: I'm presuming that the front does not have necessarily the active ingredient for certain on combinations on the front of the label of the package once you discard the box. That's what I'm --

DR. GILBERTSON: The immediate bottle container must have the active ingredient listed and the name of the product.

DR. WOOD: Even for combinations?

DR. CLAPP: Where is my question. The location is the issue.

DR. GILBERTSON: That's the issue, and I just pointed out --

DR. CLAPP: The location and whether or not it's single ingredient and combination is my concern. I think in the microscopic print you'll find it on the back, as I recall.

DR. GILBERTSON: Right.

DR. CLAPP: But if you're reading the front of the bottle, my question is: is it for the single ingredient items like just acetaminophen?

DR. GILBERTSON: No, combinations are treated differently than single ingredient --

DR. CLAPP: I heard that. You didn't hear what I said.

DR. GILBERTSON: I don't know how to answer it than to say that there is -- the provision is written that you have to have the immediate container with the name and so forth, and --

MS. LUMPKINS: But she's saying on the front.

DR. GILBERTSON: The front of the immediate container --

MS. LUMPKINS: No, no.

DR. GILBERTSON: -- of a combination drug.

MS. LUMPKINS: No, you just have to have it.

CHAIRMAN CANTILENA: On the front of the bottle versus the back in the small print.

DR. CLAPP: Versus the back.

MS. LUMPKINS: It just has to be there. It doesn't necessarily have to go on the front.

DR. CLAPP: That's my question, front versus back.

MS. LUMPKINS: That's right.

CHAIRMAN CANTILENA: Okay.

DR. UDEN: And there are no regulations for font size for the immediate container, correct?

MS. LUMPKINS: Not if it had an outer container. Drug Facts applies to the outermost carton. If there is no outermost carton, then Drug Facts would apply to the bottle and font sizes required by Drug Facts would apply there.

CHAIRMAN CANTILENA: Yes, go ahead, Dr. Wood.

DR. WOOD: I have a question for Dr. Lurie, who looks like he's leaving.

When you were talking about the U.K. rules, you focused on the package size, 16 and 32.

What you didn't mention was the other thing that they introduced, was that you had to dispense it in a blister pack.

And it's likely that that was at least as effective, given the Australian experience, as the restriction on the package size. Would you like to talk about that?

DR. LURIE: I'll take your word for it on that. I understood that not everybody implemented blister packs, even though most people did, in fact, do so. So I agree it would be hard to separate out those two effects.

No. I do, again, though think it's a very important experience with a number of studies now showing important benefits in, you know, all of the realms you'd be interested in, from hepatotoxicity, to the blood levels, to transplants, and ultimately death.

So it's a very important experience and one that I think holds important lessons here.

CHAIRMAN CANTILENA: There's a follow-up question on that, and then Dr. Davidoff.

DR. WOOD: Just to follow on the U.K. experience while this discussion is going on, I saw a paper in reading up for this meeting and that I want

to make sure I understood correctly, and I thought that paper in reviewing the U.K. experience showed that, in fact, there was a substantial increase in GI bleeding and associated deaths following that restriction on the packaging of acetaminophen.

And I just wonder whether anybody knows if that's the case and if I understood that correctly. And, again we have been discussing this channeling issue, and the presumption was that that was due to channeling of high risk patients to NSAID therapy.

Does anybody know if that was, indeed, the case?

DR. KATZ: Well, just to focus again on the packaging issue, there are data from Australia, you know, very convincing data that actually looks at antidepressant packaging and tricyclates (phonetic) antidepressant packaging, and that was put into blister packs that shows a clear and dramatic reduction in use of tricyclates in overdose.

With tricyclates, you know, it's harder to sort of make a dramatic gesture that says, you know, you don't love me as you press out 50 tablets than it is to sort take a bottle and swig it back, and so there's this sort of intuitive reasoning, I think, that seems attractive and borne out by data, which is

always reassuring, which speaks to the issue that was talked about earlier, that we're not just talking about unintentional poisoning. It's also important that we try to prevent death from the intentional poisoning, too.

DR. LURIE: Absolutely. That's, in fact, the majority of cases, and, again, I do think it's important for the committee to get away from the sometimes stereotypical notion that nothing can be done for people who attempt or succeed in committing suicide.

People are impulsive. People regret what they do. People often just jam as many pills of whatever kind they can into their mouths. They don't say, you know, this is the recommended FDA -- you know, this is the toxic dose according to the FDA. This is how many 500 milligram tablets I'll take.

They take as many as they can get without knowing the dosage pool and they stuff them in. And the more difficult you make that for them, the bigger impact you're going to have.

CHAIRMAN CANTILENA: Okay. Thank you very much.

We have a question from Dr. Davidoff.

DR. TEMPLE: Mr. Chairman, could I just

recommend there's a Dr. Daughin right behind me from England who knows what's going on, and he's a toxicologist if you want to know what's happening now in terms of --

CHAIRMAN CANTILENA: Okay. Actually, if I could hold on that because I think Dr. Davidoff has been waiting for quite some time, and then we'll come back and answer that specific question.

Go ahead, Dr. Davidoff.

DR. DAVIDOFF: Well, I actually had two quick questions, I think. The first was for Dr. Erush, and that was I thought her data were pretty interesting because they seemed to be a big more solid perhaps than some of the other, more second hand data.

My question specific was: what percent of the people of your 40-plus patients actually took doses as near as you could tell that were within the guideline, the therapeutic guideline for OTC use?

DR. ERUSH: That were within four grams per day?

DR. DAVIDOFF: Yes, right.

DR. ERUSH: I can't give you a percent. I'd say that it was probably two or three that were at or below the recommended dose.

DR. DAVIDOFF: And how reliable do you

think that information is?

DR. ERUSH: Well, if you remember, because I think I do, from our slide, I think in the unintentional group, it was about 34 percent where we were 100 percent certain of what they had taken. And we had another group where we could estimate a range, and then some we absolutely didn't know.

I don't remember exactly which group those fell into.

DR. DAVIDOFF: But it does appear to be from what you were saying that there were at least a few patients who reliably --

DR. ERUSH: Yes.

DR. DAVIDOFF: -- took four grams or less.

DR. ERUSH: Yes, I would assume that there is.

DR. DAVIDOFF: Right. The other question I had had to do with the Drug Facts because it wasn't clear to me whether everything that's in the Drug Facts information that was handed out to us is required to be somewhere on the package, either the bottle or the outer package, including the statement about acetaminophen may cause liver damage.

Is that required to be on or where is that required to be or is it required to be anywhere?

MS. LUMPKINS: Right now it's not required. Right now it's not required to be anywhere because we're still in the midst of the rulemaking. If it were to be required, it would be included in Drug Facts at the very least and maybe somewhere else.

DR. LAINE: So this alcohol warning is not on the package now?

MS. LUMPKINS: It's in the Drug Facts.

DR. LAINE: It's just not --

MS. LUMPKINS: Yeah, it's required.

DR. LAINE: It's just not in this format, but it is there.

MS. LUMPKINS: He was talking about a different -- he was talking about an overdose liver warning, but the alcohol warning is a required part of Drug Facts.

DR. LAINE: Oh, I thought he was talking about alcohol warning, but okay.

DR. GANLEY: Just to clarify, the alcohol warning was the proposed rule in 1997, finalized in '98. Okay? There was a recommendation, if you remember, by the panel. If you take an overdose, that may lead to severe -- that is not required though.

MS. LUMPKINS: Right.

DR. GANLEY: So there's two different

things. One is associating with alcohol, and the other is associating with overdose.

MS. LUMPKINS: This is where it falls in the labeling of Drug Facts, right here.

CHAIRMAN CANTILENA: So the Drug Facts is the current labeling by law.

MS. LUMPKINS: Yes.

CHAIRMAN CANTILENA: It's in the process of implementation.

MS. LUMPKINS: It's required.

DR. GANLEY: But the liver warning is not required.

MS. LUMPKINS: The liver warning is not.

CHAIRMAN CANTILENA: Right. The alcohol is part of Drug Facts, and that --

DR. GANLEY: Yeah, the alcohol liver warning is.

CHAIRMAN CANTILENA: -- is in effect, but the liver is not.

Okay. Speaking of liver, perhaps we can talk about -- just get that follow-up from England, just to answer Dr. Wood's question, and then we will proceed.

DR. DAUGHIN: My name is Paul Daughin, and I'm a toxicologist from London, and I can comment on

both the British perspective in terms of pack size and also the Australian perspective on pack size and it happened in Australia.

In the U.K. in September '98, there was a change to maximum sales of paracetamol in a fan (phonetic) of 32 tablets or blister packs in pharmacies, 16 tablets in non-pharmacy outlets, supermarkets, street-side stores.

There have been a number of studies that have tried to look at the impact of that. There's definitely been an impact on severe overdose, about a 20 percent decrease in the number of deaths from paracetamol in the year after the legislation was brought in, and a decrease in the number of referrals to liver transplant units.

The problem is those are relatively small numbers, and so it's difficult to know whether we're seeing a real effect or not.

When you look at the other end of the spectrum, the non-severe overdoses, there's been a much less significant impact. There are about 70 to 80,000 overdoses per year in the U.K. There's perhaps been a two or three percent decrease in the number of overdoses overall.

There's also been data that's looked at

the number of sales of over the counter analgesics. Paracetamol sales have decreased from 300 million a year to about 150 million a year. Ibuprofen sales have increased by a factor of about 70 to 80 percent. Aspirin sales have fallen slightly.

If we then look at Australian data, during 1999 and 2000 there were two incidents where paracetamol had to be removed because of problems with contamination. A poison service and a clinical toxicology service looked at cases that were presented to them of overdose, both deliberate and accidental. There was no overall change in the number of paracetamol overdoses, but there was a significant increase in the number of ibuprofen accidental poisonings that were reported to the poison service and a significant increase in the number of aspirin poisonings in the clinical toxicology service, suggesting that the decrease in the number of paracetamol sales was perhaps shifting things to ibuprofen and other nonsteroidal agents.

So data from the U.K. and the Australia just to give the wider perspective to it, and to reiterate, in the U.K. what we've seen is a decrease in the sale of paracetamol with an increase in the sale of alternative analgesics.

CHAIRMAN CANTILENA: Okay. Thank you.

I think Dr. Brass has a follow-up.

DR. BRASS: Yeah, just to make sure I understand. When you said there was a 20 percent decrease in the number of severe poisonings, was that corrected for the change in sales denominator?

DR. DAUGHIN: Yes, that was.

DR. BRASS: So the rate per --

DR. DAUGHIN: Yeah, the rate had fallen.

DR. BRASS: Thank you.

DR. DAUGHIN: But to reiterate, there are relatively small numbers, and we've only seen two years of follow-up, and so there may be fluctuations in the data, and we don't know whether we've seen a real change or not

CHAIRMAN CANTILENA: Okay. Thank you.

What I would like to do now is actually take a 12 minute break until 3:00 p.m. and give everyone a chance to stretch, and then we're going to come back and change the program a little bit.

(Whereupon, the foregoing matter went off the record at 2:48 p.m. and went back on the record at 3:10 p.m.)

CHAIRMAN CANTILENA: Thank you.

What I'd like to do actually for the panel

members is I'm going to be passing some packages and, you know, container bottles around which demonstrate new packaging which I understand has been available for two to three months, which goes over some of the things that we've talked about, and again, this is just for one of the sponsors. It isn't obviously for the generics, but I think it actually addresses some of the comments that were made, and we'll just pass that around. Just if you can pass it that way and then back across.

What I thought we'd do to avoid the possibility of being here until midnight if we followed the prescription or the points to consider that we were given is to change a little bit and to sort of, you know, focus the discussion into several specific areas, and I realize there's a lot of overlap between the topics, but what I would like to propose is that we start to talk about unintentional overdoses and some of the factors, and then get into the labeling.

And I'll actually ask the question: do people favor changes to the label now or should we hold off until there are more studies done?

And if yes, what type of changes to the label? If you want to do it now, then what type of

changes should we make now?

And we have some choices that were given to us on the sheets from the points to consider.

Then I thought we would separate out the drug-drug interactions and subpopulation question, people with, you know, liver disease, et cetera, alcoholics, into a separate discussion, realizing that some of that does impact on the issues for labeling, but I would like to separate that.

And then if anyone is still breathing, we can then take up the issue of combination for, you know, the Rx drugs and talk about that.

And then lastly, end with exactly what was requested by FDA, which is Item 5: what additional studies are needed, if any, to evaluate the issue?

So actually let me just start with a question, and I think for the first question I will just do sort of a yes/no, and then we can have an open discussion about factors. When I do the labeling question, I intend to go around the table so that every individual will have an opportunity to comment on the reason for their vote or specific factors that they feel are most important for the question, or if they wish, they don't have to comment and they can just vote. Either way, that's fine.

So we will get into the labeling as sort of the second issue, but I guess the first question was in general by show of hands: as we sit here after we've heard, you know, everything from the sponsor, from FDA, et cetera, et cetera, and from what we know from the packets and our own, you know, expertise, do we feel there is a significant issue regarding unintentional overdose that should stimulate action by FDA to try to, you know, decrease the occurrence of unintentional overdose?

I'm specifically using the word "action" because if we say change in this or change in that, that's a whole separate, you know, topic. So I would just like to get a feel for where people are.

If the vote to this is unanimously no, then you can easily make happy hour.

(Laughter.)

CHAIRMAN CANTILENA: And we're probably done for the day, but if it's not unanimously no, then we'll go on to the other issues and actually talk about it.

So again, the question: is the issue of unintentional overdose as we have heard it, you know, worthy of action by FDA as we sit here today?

If you are in the affirmative, if it is

worthy of action, if you can raise your hand, please, and we'll actually take a count.

(Show of hands.)

CHAIRMAN CANTILENA: Okay. I think we're unanimous. Was there anyone voting in the negative or abstaining?

(Show of hands.)

CHAIRMAN CANTILENA: Okay. So there goes happy hour. Okay.

(Laughter.)

CHAIRMAN CANTILENA: All right. What I'd like to do is actually open the discussion to look and actually concentrate on some of the factors that were, you know, listed for us in point number one for the committee discussion, the possible factors.

And, again, we are going to specifically talk about, you know, labeling in sort of the next section. So you can talk about it, but really don't, you know, focus.

But just a general discussion of what people feel are the most important factors that are contributing to unintentional overdose, and I'll just open it up and we'll start around the table.

Dr. Cush.

DR. CUSH: The issue of unintentional

toxicity could also be regarded as uneducated toxicity. So I would make the proposal that all these packages, whether it's single product or combined product or even prescription product, have the bold label that this product contains acetaminophen.

Moreover, I'd also maybe even go so far as to say that we should take about more of a bold, big box warning just like the Surgeon General's warning for tobacco, saying the combined use of acetaminophen containing products may be harmful to your liver.

CHAIRMAN CANTILENA: Okay. I think Dr. Brass is next.

DR. BRASS: I'm going to preface my remarks now and actually say it for all my subsequent remarks this afternoon, that I'm really cognizant of the fact that on a given answer, it's not going to be based on the compelling data that has been presented. Rather, it's going to be based on common sense, a gestalt of the information and my own clinical experience and what I understand about acetaminophen hepatotoxicity.

And so that will make my ability to defend my answers somewhat more difficult than I normally feel. Having said that, I think there are four areas that strike me as being relevant. One is the use,

unintentional use, of multiple acetaminophen containing products.

Two, exceeding the recommended dose with under appreciation of the consequences of exceeding the dose.

A third issue we didn't hear a lot about today, but we've heard about previously is misdosing of infants and the difficulty in proper dosing of infants.

And the fourth issue is related to subgroups as yet to be defined, and I'll hold off on that.

And I will also add another caveat from my perspective. As we think about these and potential changes, I will also point out that we actually don't have a lot of data that tells us about the efficacy of risk management in the OTC setting, the effectiveness of warnings on labels, how to modify consumer behavior in the OTC setting. So we'll be making that up as we go along as well.

CHAIRMAN CANTILENA: Thank you.

Dr. Williams.

DR. WILLIAMS: Well, I would support everything Jack Cush suggested. I think there needs to be clearly stated that acetaminophen is in these

products, and that the patients need to be educated that combinations of acetaminophen containing products can exceed the allowable dose, and that would be the only thing that I would add to it, is that there needs to be a continued patient education process like that Med Be Wise or whatever to let the patients know that acetaminophen isn't totally benign.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Elashoff.

DR. ELASHOFF: Yes. I think a major issue has to do with the efficacy labeling of even the single product because if you buy the bottles with the 325, it says take two every four to six hours. At least that's the bottle I got.

If you get the one for 500, it says take two every four to six hours. Those can't be both good advice.

In this oral surgery study, they talked about 60 percent of people took another 1,000 milligram dose in less than four hours, and it says the duration of a single dose was three to five hours.

So if you start taking the 1,000 milligrams every four hours, what do you do by the time you get to the 16 hour point and you're not supposed to take anymore in the 24 hours?

It leaves people hanging. So I think that whole business of the efficacy labeling contributes to the probability of taking an overdose and needs to be looked at.

CHAIRMAN CANTILENA: Thank you.

Dr. Katz.

DR. KATZ: Two points. The first is that although the data is really amazingly weak in terms of understanding exactly what the magnitude of causal connection is between acetaminophen and acute liver failure, it still seems obvious to me that from a labeling point of view somebody should be able to buy something in the supermarket and know what's in it.

And one of my more boring hobbies is that I'm interested in the history of opioid therapy, and I was reminded during this conversation of the fact that in the late 19th Century, you could go to the pharmacy and be sold a bottle of something that contained ten percent morphine without there being any requirement at all to put on the bottle exactly what was in it, even if it was a treatment for opioid addiction.

And so it strikes me that we're talking about something very similar, and that we may look with horror, you know, back on those days, but now it doesn't really seem that different.

So I would propose, and I think that it would be relatively straightforward to achieve consensus on this, that the name of the medication should be on the bottle itself and not just the package, with a list of every ingredient that's in it and know what it's for in terms of the concentration in a size font that's readable.

To me that doesn't seem like a radical notion, and so that's my first point.

My second point is that, on the other hand, lack of effective pain management is a huge problem in this country, and I think as we were talking about putting warnings on labels, we don't want to make Tylenol look like a dangerous drug.

The person that I'm worried about is the little old lady who is going to say, "Oh, now, look at this warning. I'd better not take my, you know, few Tylenol a day for my arthritis, and I'd better sit home and suffer again."

We certainly don't want people who are most vulnerable due to under medication of pain to be adversely affected and then the balance actually have a negative impact on public health.

CHAIRMAN CANTILENA: Thank you.

Dr. Clapp.

DR. CLAPP: I have concerns about the dosing of acetaminophen for pediatric patients particularly, considering the milligram per kilogram dosing that we as pediatricians recommend.

One of my concerns is that in adult strength Tylenol the recommendation is for children 12 years and older to take two 500 milligram gelcaps every four to six hours, along with adults, and the variation in 12 year olds' weight can be all across the map.

You can have a 65 pound 12 year old who's a petite person, as well as 200 pound 12 year old. I'm wondering about some of the studies done, particular the pharmacologist from the University of Pennsylvania that said there was some identified cases that had no clear-cut etiology as to the nature of the risk factor for toxicity.

I'm wondering if perhaps in adults the little old lady that you suggest, perhaps it might be that adults also have some issues concerning weight and milligram per kilogram dosing of Tylenol.

So that in addition to putting age recommendations, that across the board weight be a consideration for instructions in dosing acetaminophen.

CHAIRMAN CANTILENA: Thank you.

Dr. Patten.

DR. PATTEN: Yes. I'll speak for little old ladies.

(Laughter.)

DR. PATTEN: I think that little old ladies are fairly heavy users of professional health care providers, and so that is a wonderful subpopulation for health care providers to assist then in making these kinds of decisions.

So physicians, nurse practitioners, and so on, who are seeing little old ladies as patients will have a wonderful opportunity to make sure that they're not overlooking or rejecting acetaminophen as an effective pain medication.

So much emphasis in medicine today is on prevention that as I'm starting to think about reconfiguring labels or having new information on the labels, I'm thinking about it in terms of a preventive measure.

And so, therefore, I'm not quite so worried about quickly assessing efficacy. Efficacy of other kinds of preventive measures often aren't assessed until long down the road.

Thank you.

CHAIRMAN CANTILENA: Thank you.

Dr. Cohen.

DR. COHEN: Yeah, I wanted to mention a few things that we really haven't discussed yet that might be contributing to some of the confusion and unintentional overdoses.

First of all, I also obviously agree that it's important to have the ingredients of all of these products clearly listed, and I think it's important to understand what type of background might be needed to bring this information out, just printing it on a white background.

I mean, I saw, you know, a modification of the label as displayed in the other room, and it looked pretty good, but I think we could do better than that, and I think that should be part of the requirement. The font size, et cetera, needs to be looked at.

I know we do that with prescription drugs, for example, where the size of the nonproprietary name has to be half the size of the brand name, and perhaps we could look into something like that for this.

The brand extensions, as I mentioned earlier, I think they're important to contain this information, and I note that quite a few of these

products actually do take space now to say that they're not aspirin, the non-aspirin product or does not contain aspirin.

I think the statements in the labeling now, the dosing under two years old, call your doctor or if you had more than three drinks or take more than three drinks, call your doctor. At the minimum I think it should also say your pharmacist, not just your doctor, because in many cases they're going to be more accessible.

But more than that, I think it's really important and we haven't really discussed it all that much yet, is the idea of having actual dosing for people that are under two years old, little ones.

We need that. People need to know what to do because they're not calling their doctor in some of these cases. They're taking it upon themselves. If their child has a fever, they're not going to wait until somebody actually calls back.

I think the extended release products need to be looked at and the dosing of them. They're not always being administered as they were intended. They are sometimes given Q four hours or Q six hours. I know some health professionals have actually made that mistake.

I think the statements in the labeling, droppers full, are confusing when we're talking about the infant concentrate product, and I don't mean to just indicate that McNeil is the only manufacturer. We have seen generic products that have that same product as well, and the term "droppers full" to a lot of people means a full dropper, not the actual measurement that's on the dropper itself.

The safety lock product is extremely important. we saw data in our packets that has really helped to reduce the number of overdoses with that concentrate. Yet the generic manufacturers do not have this product.

And I think if it it has worked so well and we're going to continue to have that product on the market -- and I know that's probably something we also should talk about, the concentration that's available -- then I think we ought to require that from all of the manufacturers, however that's done.

One other thing. The way that the concentrations are expressed on the liquid products, if you look at the label, I don't know if we have them here, but you'll see the concentration is actually expressed as a 160 milligram per on both the concentrated product and the children's product.

In other words, it's 160 per five mL, and the other one, I believe, is 160 per 1.6 mL. But what the consumer might see if they were looking at them both at the same time on a shelf next to one another is that they both are the same concentration.

I think that the way that that concentration is expressed could be a lot clearer, and so I think that's something also that we should be looking at.

Thank you.

CHAIRMAN CANTILENA: Okay. Dr. Wood and then Dr. Furberg and then Dr. Cush.

DR. WOOD: I tried in my own mind to break this down into three sort of subheadings, and I had the Brass sort of preamble first, I think, where I'm working on sort of intuitive reasoning as much as databased reasoning.

But it seemed to me there were sort of three headings moved forward: prevention of confusion making it harder to take an overdose, and labeling for subgroups.

And you've taken the last one off the table for now, and I'll respect that.

The prevention of confusion, it seems to me that we need to certainly include labeling for the

ingredients on the front, but it seems to me we ought to consider going further than that because for the combination products, there's multiple ingredients, and they all have long names, and certainly most of the people I know, they would just blank out on that.

So I think there may be a need to have something that sort of calls out, contains acetaminophen. If it's reasonable to say it doesn't contain aspirin on the front label, it's probably equally reasonable to say it contains acetaminophen because what you really want people to know is that when they line up three bottles and they're about to take tables from each of these, they need to understand that each of these contains acetaminophen and that there's going to be an additive effect from that. So I think it's not just listing the ingredients. It's calling that out somehow.

The third thing in avoiding confusion, it seems to me, is limiting the number of doses, the different dosage forms that are available so that particularly in children there's not multiple concentrations available, and the issues of the 350 and the 500 and so on have been talked about before.

Then the second heading was making it harder to take an overdose, and it seems to me, again,

we have to work on somewhat intuitive reasoning, but I think we have a duty to prevent people dying from acetaminophen however they get there, and I think we need to address both the people who in a gesture or whatever take too much acetaminophen or those who get there by taking too much accidentally.

And I don't make as big a distinction as other people perhaps have made of that, and I think blister packs clearly would help in that, and the data that was presented from the U.K. which was presented, I guess, to speak against that seemed to me to only speak more compellingly in favor of that.

There's not much we've managed to do as physicians that have reduced the frequency of overdoses in any situation than the fact that we've done that.

So I think dealing with the blister packs also allows you to put the "contains acetaminophen" wording right at the point of use as well.

The labeling from subgroup issues I'll leave for now.

CHAIRMAN CANTILENA: Thank you.

Dr. Furberg.

DR. FURBERG: Yeah, I'd like to extend what Dr. Cohen said, that we should rest the liquid

formulation. I think we really should pursue standardization of that and so to avoid unintentional use.

And also I agree with Dr. Wood. Blister packs, I think, is the way to go, but in order to keep the level playing field, let's look into that in a broader sense, and that could also apply to other pain killers.

CHAIRMAN CANTILENA: Okay. Thank you.

Actually I have a question for Dr. Ganley.

The issue of standardization of concentration, are there other factors such as, you know, the volume, you know, like in a specific age group that have, you know, resulted in the concentration issues that we're discussing?

DR. GANLEY: I'm not sure if you're asking standardized concentrations or the volume allowed in a bottle.

CHAIRMAN CANTILENA: Not in a bottle. In terms of, you know, like a dose. Is there background information as --

DR. GANLEY: You mean the total doses in a bottle.

CHAIRMAN CANTILENA: -- to why we have, you know, different concentrations?

DR. GANLEY: Well, I guess the easy answer here is that's what the free market is right now. You know, the only example that I can think of in this country that has a limitation on the package size is sodium phosphate, and that was based was based on problems with the 240 mL bottle where people were running into problems with various metabolic abnormalities because they would drink the whole bottle.

And that's been cut down in size, and it's still been somewhat of a little bit of a problem for us, and we're going to make some changes in that even and cut it down to 45 most likely because people are still taking 90 and getting into problems.

But there there was something that we could specifically point to and identify that there was a problem. It becomes more problematic for us when we want to put limitations on package sizes and, you know, the way these monographs are written, various dosage strengths and things like that because we have to provide some data that would justify it for us. Okay? We can't just do it on a whim.

And so, for example, if people thought there should be a package size imitation, we really have to go into U.K. and find out really what is the

story going on there.

And we've heard different opinions today of what's going on, but we'd have to go in and actually get data or go to Australia and get data and then use that as a basis if we were going to go down that route.

But we just can't say that this committee thought that you should only have 30 tablets in a package size because a lot of these -- you know, a rule like this would have to go through various clearances at OMB, and if we don't have data to support that, you know, there would have to be -- it's very difficult to impose that on companies, I think.

DR. WOOD: That was not what I was proposing. I was proposing blister packs, not a limit on the --

DR. GANLEY: But my point is that we need to find out. I talked to someone in the U.K. the other day, and I got a different impression of how successful this has actually been from what's been said today.

I'm not going to state that I really think we need to go and talk to the regulators in the U.K. and really find out has this been a successful program.

CHAIRMAN CANTILENA: Okay. Dr. Cush and then Dr. Brass.

DR. CUSH: To get to the pediatric issue, I think that I would support the comments thus far made. I would actually go so far as to say that we should really say that all of these preparations we're talking about today should really have the label, and that this is a problem for adult use only, and that if there are products to be marketed to children, that they should go under a separate product, a separate box, and they should be pediatric formulations to avoid children using adult doses and getting confused in that situation.

Also, I'd also suggest as far as education that avoidance of the abbreviation APAP, and I think it's more in the prescriptive end rather than the OTC end, would also go a long way in avoiding a lot of confusion.

DR. GANLEY: Can I just follow up on that a second?

I can tell you one of the problems we're running into now with manufacturers through the NDA side is they will have a single formulation that they package, and it will have dosing that includes adult dosing and children dosing, and what they want to do

is take that exact same formulation and make a children's package.

It's the exact same formulation. Everything is the same, and that's the problem we're sort of running into. We've been reluctant to try to do that because you could actually carve out the elderly package, the adolescent package. It's just innumerable how many different things you go.

And so we've sort of said, well, there's no difference here from this adult package, and you're just throwing this children's package on the market now, and that's going to lead potentially to some problems because you could create five other, you know, various package groups.

DR. CUSH: I don't think that we heard that the LD was a particular issue, other than that these were the main users of these drugs. We did hear that children are a separate issue and how they get into trouble. This is what might address that.

I think if you have separate packaging, it avoids the ability to look at adult dosing and kid dosing and, well, my kid is kind of a big kid. So I'll give him the adult dose.

And I think if you just go for a pediatric package, it just has labeling for that child or

children up to the age of 16 or it could be on a per kilogram or per poundage weight basis.

DR. GANLEY: Well, one of the things you did say in the first comment was that you mentioned a pediatric formulation. But again, one thing is that if you go down that route, you have ten companies that market something and you multiply that potentially just by four or five, and you have a children's product and an adult product.

I mean, I'm not arguing with you. I think it's something we need to look into to see is that something that is a worthwhile measure, but the potential is that, you know, you just have a reproduction of the same product, but in a different package.

DR. CUSH: But the goal, of course, would be to prevent pediatric accidental overuse.

DR. GANLEY: Right.

DR. CUSH: And if that's a measure that would work, then I think it should be employed.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Brass.

DR. BRASS: It seems like we're moving on to some of the specific labeling suggestions, which I thought you were going to separate out.

CHAIRMAN CANTILENA: We actually are. After two more questions, we'll have a vote, and then a discussion.

DR. BRASS: Okay. Then I have a question of clarification apropos of this. Acetaminophen containing products actually are available in the U.S. market in a variety of package sizes, forms, and I think including some blister pack things.

Now, clearly consumers are selecting them for different reasons, but it would be interesting to know whether or not those products are being used preferentially in suicide attempts, et cetera, and at least understand the data within our own system, as well as collecting that additional data.

CHAIRMAN CANTILENA: Okay. Comments from Dr. Williams and then Dr. Alfano.

DR. WILLIAMS: I just wanted to speak against blister packing requirement. As a rheumatologist, several of my patients that use acetaminophen also have disease of their hands, and blister packs would make it even more difficult for them to use these products.

CHAIRMAN CANTILENA: Dr. Alfano.

DR. ALFANO: Yeah, my comment is sparked by I guess something Dr. Brass said, which many people

seem to share, that he feels compelled to offer comments based primarily on sort of intuitive reasoning. I think DR. Cook also seconded that concern.

And I think we should make those comments based upon disintuitive reasoning. My concern is that we not take that intuitive definition of the problem and combine it with empirical solutions that we really have not evaluated yet. So we need to be really careful because they won't cancel out the soft data on either end.

And it really leads me to comment along the lines of the way we teach our medical students, which is first do no harm, which is not to say do nothing, and you know, there's 24 billion doses of this product sold each year, and therefore, a little change unintentionally could make a big difference. So we really do need to be careful.

Also, we have seen some formidable changes by the manufacturer in the readability of the label and to its credit, it's at the expense of the sell on the label. It may not go far enough, but it's definitely moving in the right direction, and we ought to see how that plays out, as well as the industry-wide introduction of the Drug Facts label moving

forward.

I was intrigued that we're also starting to get some prospective data now from Dr. Lee and Dr. Erush, and that type of data, I think, can go a long way in terms of interacting with the people who have actually had these unintentional overdoses so that we can understand the cause of them and then on that basis design better labeling.

The other databases don't allow us to interact with the patient or the consumer and, therefore, we could stumble. So clearly there's the need for improved labeling, improved consumer education.

As I think back to the Reye's Syndrome, success where the problem was reduced by an order of magnitude. I don't think it was simply the labeling. It was the consumer education and public relations that went with that.

Thank you.

CHAIRMAN CANTILENA: Thank you, Dr. Alfano, for your comments.

Dr. Crawford.

DR. CRAWFORD: Thank you.

Very quickly, I'm very much in support with most of what's been said in this discussion. I

just want to point out the fact that we shouldn't be presumptive to assume that even the majority of consumers who would consume the product know the word acetaminophen, those six syllables. I think it is much more known through the predominant brand name, and the only reason I bring this up is that any efforts that this committee might recommend to the FDA I think we should also say it's part of broader educational campaigns to inform consumers what is acetaminophen. Because most people know what aspirin is, but no by that name "acetaminophen."

CHAIRMAN CANTILENA: Okay. Thank you.

I'd now like to shift gears slightly, although we've already started to touch on it. Oh, I'm sorry. Dr. Johnson.

DR. JOHNSON: I had a couple of comments. One was in relation to, I think, sort of what can be done, and one of the points that really hasn't been addressed is education of professionals, and my guess is that physicians and pharmacists would be fairly surprised, as I was, not at the suicidal intentional overdose and the impact of that, but at the unintentional overdose and the potential risk of that.

And so I think that along with consumer education, it's really important that there's also

professional education to really heighten people's awareness that smaller than perceived risk doses may be risky for certain populations.

And I'll save my other comments for later.

CHAIRMAN CANTILENA: Okay. Thank you.

One more comment on this from Dr. Davidoff.

DR. DAVIDOFF: Yes. Aside from generally supporting the intuitive or you might say Bayesian notion that it makes sense to let people know exactly what they're taking, I think that there is this issue of are there high risk populations in some sense. It's quite important because a lot of the thinking about what to do seems to hinge around the question of whether they're are potentially identifiable.

Having heard all of this through all of this information, my sense is that there appear to be some higher risk patients. The problem is that we haven't figured out -- I really don't think we've figured out how to identify them, and part of the clue may be in some of the data that was presented from the University of Pennsylvania study.

Because it's beginning to me to look like it may not just be a factor, an additional risk factor per patient. It may be a multiplicity of additional

risk factors that really begins to matter.

That being the case, it's going to be really difficult to pin that down, but I think at this point it is reasonable to say that there are some patients who are at increased risk, and I don't see any reason why that kind of a statement couldn't be captured and not be distorting the information that we do have.

One of the concerns I have about the way the alcohol warning is now written is that the statement about potential liver toxicity is tucked in under the alcohol warning, making it look as though it's the patients who drink who are at risk.

But from PEN data and lots of other information, it looks like that isn't the only additional risk factor. So I would urge that consideration be given to having a liver toxicity statement separate from the alcohol warning.

CHAIRMAN CANTILENA: Okay. Thank you.

If we can now sort of continue our conversation about the labeling, what I'd like to get is a yes/no from the panel on whether or not you favor changes to the label now versus waiting for further studies to be completed.

And let me just, you know, define by th

regulatory definition of now. Dr. Ganley, perhaps you can tell us --

(Laughter.)

CHAIRMAN CANTILENA: -- how long it took to change the label after the panel voted in June of '93 for the alcohol warning.

DR. GANLEY: I think you could have subtracted from the slides, Lou. It was '98 that the final came out. '97 was when the proposal went out. So it was a four-year period.

I think we'll act a little more promptly now because really this, you know, is an important monograph to get done, and we're committed, I think. The whole agency is committed to get it done, and so I think any recommendations that you make will, you know, encourage us to get it through the regulatory process as quickly as possible.

CHAIRMAN CANTILENA: Okay. So the initial question is, you know: do you favor changes to the label for all acetaminophen products now, or should those changes be held until studies are completed and analyzed and we have more information to go on?

And if you vote yes, perhaps in your comments if you wish, can you specifically highlight some of the things that you would like to change now

in the label versus perhaps, you know, something that we can hold off on for however may years the studies will take, et cetera, et cetera?

So what I'd like to do this time is start at the end of the table here with Dr. Furberg. If you can first vote, you know, yes or no, and then if yes, highlight, you know, specifically the information that you'd like to see in the label.

DR. FURBERG: My vote is yes, and I would like to see the ingredients on the container readable, in bold.

CHAIRMAN CANTILENA: Okay, and then we were passing around these bottles, which are relatively new to the market. So I guess maybe if you can recall, is something like that, you know, what you were talking about or, you know, something else?

DR. FURBERG: Something like that.

CHAIRMAN CANTILENA: Dr. Crawford.

DR. CRAWFORD: Thank you.

My vote is no, not right now. Ultimately yes for changes in labeling. I would like to see more empirical studies on issues such as comprehension, understanding, readability for consumers, literacy levels and how that might affect it both for the labeling and possibly for the packaging.

CHAIRMAN CANTILENA: Dr. Cush.

DR. CUSH: I vote for a change now, and any product that contains acetaminophen should say "contains acetaminophen" in a font and size that is at least 50 percent of the major label of the brand name on the box or bottle and that there also be even another box. It may take up the whole side of the outside package that says "warning: combined use could be associated with increased toxicity."

CHAIRMAN CANTILENA: Thank you.

Dr. Elashoff.

DR. ELASHOFF: Yeah. I essentially agree with that, although I would like to see the actual dose more prominent. One of those you have to keep turning and turning around the box to find where the dose is. It took me a couple of minutes to see that the dose was actually there. It was tiny print on an end of the box that you wouldn't even think of looking at.

So I think the dose needs to be more prominent, especially since there are two different strengths on the market.

CHAIRMAN CANTILENA: Thank you.

Dr. Watkins.

DR. WATKINS: I think the labeling change

should be now, and I think the key thing is that acetaminophen be clearly noted on the front of the box and on the bottle, and then definitely education efforts to be made to get people to understand what acetaminophen is and the danger of combining products.

I get a little concerned about the equivalent of a black box warning just because I think it may scare people away from the product unnecessarily, but the idea of the education, I think, is the important thing and exactly how to do that I'm not sure.

CHAIRMAN CANTILENA: Dr. Brass.

DR. BRASS: I'm going to vote now with an asterisk, and that --

CHAIRMAN CANTILENA: Why am I not surprised, Dr. Brass.

(Laughter.)

DR. BRASS: Because I'm a little concerned and actually agree with some of the other comments that I'm very clear in my mind what the problems are that need to be addressed in the label. I'm less clear what the best way to address the problem is.

And, therefore, I would like to see some fast track validation that whatever change is implemented really addresses the problem.

So, therefore, my first problem is to insure the consumer knows that the product contains acetaminophen and not to combine it. So I do agree that the front of the package must say "contains acetaminophen," and I would also add a warning that says "do not use with other products that contain acetaminophen" so that that is crystal clear. So somehow that's message one.

Message two is that this is not a benign product, and that the recommended dose is a recommended dose. So under the directions I would try to convey something like "do not exceed the recommended dose unless directed by a doctor. Exceeding the recommended dose may cause liver damage," or something that makes it clear that it shouldn't be done, and it's not a benign thing.

Again, whether that's the best way to do that I don't know, but something like that.

And then the third issue, which I actually don't even have recommendations on because I don't know how to do it, is the dosing of infants and children that minimizes the incorrect dosing, whether that's standardization of preparations, reexpressing the label. I don't know how to do that, but something has to be done now to minimize those incorrect dosing

regimens.

CHAIRMAN CANTILENA: Thank you.

Dr. Davidoff.

DR. DAVIDOFF: I would endorse going ahead now. I really don't have a whole lot to add to the recommendations that Dr. Brass brought up.

I also agree, however, that some sort of education in the broad sense is really quite important. I think the NCPIE data and other data do indicate that consumers tend not to read labels, not to read them terribly carefully. They don't tend to understand them well.

Labeling is all very well, and certainly saying that every product that contains acetaminophen contains is potentially valuable, but only potentially. And I think that as with the Reye's Syndrome experience, that a good deal of the benefit seems to have accrued from things that went beyond labeling.

So I would strongly urge that there be the changes, but that that education be somehow built in.

CHAIRMAN CANTILENA: Dr. Lam.

DR. LAM: I would vote for changes right now, and to me there are two issues that concern. Number one is the lack of appreciation of toxicity and

the lack of appreciation of what would be the reasonable and appropriate use.

And as I look at the label given to us by the FDA and think about what I would do, normally if I pick up a package, the first thing I would do is to go for how to take the medicine, the directions, and under the direction it said do not exceed 12 caplets in 24 hours. And I would think that would be the place to actually tell them what would happen if you take more than the recommended dose.

During the experience on dealing with kids, telling them don't do that is less effective as telling them don't do that and explain to them why you don't want to do that.

So I presume that do not exceed the recommended dose or the maximum recommended dose with an explanation, which really doesn't take that much wording in there should be the way to do it.

CHAIRMAN CANTILENA: Thank you.

Dr. Cryer.

DR. CRYER: Without repeating several of the comments that have been made, I agree with many of the things. I personally see the issue of education being more important than these issues of labeling because without the education the labeling really has

minimal impact.

To emphasize some comments that maybe haven't been emphasized, I think it's equally important to make sure that whatever is implemented with respect to OTC dosing of acetaminophen or all analgesics should also equally be applied to prescribed products because in the acetaminophen case, the issue as I heard it, about a quarter of the issue was of the problems were combining the OTC products with the prescribed products. So you're really not accomplishing anything if you focus all of your efforts in the OTC arena without applying the same proposals to the prescribed issues. So I think you need to make that parallel.

And the other thing that I really want to focus on is that you should have changes now, but ultimately there has to be some sort of validation. We're all educated, sitting around making proposals as to what we think should be the best thing for the consumer and the lay population, but we don't really know.

I would propose that ultimately the FDA might want to consider as a stipulation for approval of OTC products that there needs to be some threshold level of consumer comprehension as the validation for

ultimate acceptance of that OTC product because I really haven't gotten since that that is part of the requirements.

I mean, we're kind of working in a vacuum in terms of the knowledge.

CHAIRMAN CANTILENA: Yeah. Actually, you know, for the drugs that are switched from Rx to OTC, that's always, you know, part of the information, you know, that we get, you know, actual use studies and things like that. But I hear what you're saying in terms of this specific area where, you know, these have been on the market for a long time and, you know, we don't have that information. Very good.

Dr. Laine.

DR. LAINE: I agree with everything. All of the good ideas are taken.

I would say yes, now. Just to emphasize a couple of things, what I am struck by when I look at this label is the fact that what we're all here talking about isn't listed anywhere, that is, liver disease. As Dr. Davidoff mentioned, it implies only if you drink alcohol do you get liver disease.

So, I mean, to reiterate what was said, I mean, somewhere on this label we should have a warning that liver damage can occur.

I think the harder decision is I agree with the way Dr. Brass worded it, that if you exceed the dose, the question we have to grapple with frankly is that actually ignores the unintentional or, you know, the just minimally -- the four to six to eight gram dose, and I think that's what we have to grapple with. How shall we deal with that now or should we not?

But I definitely at a minimum would at least mention that damage can occur. Use is important, and perhaps under directions we should somehow try to get across it's not only do not exceed 12 caps in 24 hours, but get across, again, the idea as people have mentioned that don't exceed a total of X amount of acetaminophen in the directions. Because just to try to make it very clear that people need to keep in mind that they may be taking multiple acetaminophen containing components.

So I'll stop there, but those two are important to me.

CHAIRMAN CANTILENA: Thank you.

Dr. D'Agostino.

DR. D'AGOSTINO: I obviously agree with so much that's gone ahead. If I didn't, people would say it's insane. But I'd just to just throw out a couple

of points here.

We're not really dealing with the zero database. I mean, the relationship between the particular overdose and the sort of latency period and then coming back and having a terrible condition, I mean, even though we don't have careful, well controlled studies, Dr. Lee's data, the AERs data, and so forth, even when the McNeil panel reviewed that, there were a number of cases that were, as far as they were concerned and as far as everyone else was concerned, clearly has a relation.

And we know the causality, and we see the problems that can develop. So I don't think we're working from, say, a zero database.

I think also that the idea of the combination not containing the product ingredients in the front is just something that has to be addressed, and that we can do.

And just to go back, I kept writing over and over again as we were talking what does the consumer do with what we've done. The point that was just raised by Dr. Cryer is that I'm concerned. We've gone through a lot of these things in these meetings here. You can put things on the label, but do the consumers understand them?

And what's going on in my mind is how do we get those labeled comprehension studies as we load up the box with all of these new warnings and what have you. How do we know the consumer is going to understand them?

And I think we will come back to that, but I just want to mention that.

CHAIRMAN CANTILENA: Thank you.

Dr. Alfano.

DR. ALFANO: Well, as you know, I don't vote, but I have a perspective that changes in the label along the line of what we saw passed around, I think are clearly in the right direction.

As far as whether there should be a specific liver warning or not, this is one of those areas where I would actually like to see what the consumer tells us. The new label actually has a warning, has an overdose warning that warns that serious health problems in the event of overdose and basically advises people to get to the Poison Control Center and physician right away.

I would be concerned that to a layman maybe liver means, once again, oh, that's for people who drink. That's not me, and you could actually make a case it might not be helpful. And here's where we

need to be careful.

Is it is more helpful or not? If it is, then we ought to say liver. If not, we ought to simply say serious health problems.

CHAIRMAN CANTILENA: Thank you.

Dr. Clapp.

DR. CLAPP: first, I'd like to say I've seen tremendous improvement on the new and improved bottle of Tylenol as compared to the box that we have here, but there are some ambiguities that I remain concerned about in the dosing on the basis of weight.

For example, with the children's Tylenol elixir or liquid form or tablets, and actually the concentration of Tylenol or acetaminophen is typically 100 -- well, is always to my knowledge 160 milligrams in one teaspoonful or per five mL, and the droppers, it's 80 milligrams in .8 milligrams -- milliliters. I'm sorry.

And intuitive reasoning that I can presume as a pediatrician is that you will have to wrestle a small baby to drink a teaspoonful of vile tasting medicine, and it's much easier to get them to drink .8 milliliters than five milliliters.

And I don't know if the drug company -- that's their intention, but the reality is it's much

easier dosing.

But in the Tylenol, children's Tylenol, it says 96 pounds and over four tablets, which is equal to 650 milligrams, but on the gelcaps, it says 12 years and older, 500 milligrams. You can take two tablets.

So there's a little bit of ambiguity here that we haven't addressed, and I'm not sure if we are then focusing on weight is the issue or age is the issue. The confusion that we are leading people to believe.

If children swallow pills, believe me, as a pediatrician they do not want to chew things that taste terrible. They don't want to drink four to six teaspoons full of something. The younger they are in swallowing pills, the happier they are.

So we need to make sure that there's some consistency that we are giving the public with dosing. I don't know if I can request information from the FDA as to toxicity in adults related to weight only as the indication because I wonder if the 96 pounds is a magic number that we see these unidentified etiologies of liver toxicity as the cause may be based on weight alone. So that's one thing.

Secondly, in reading this label it says

take two caplets every four to six hours as needed, and then the next bullet is, "Do not take more than eight caplets in 24 hours."

Well, this is intuitive, and this is where the pharmacologist is letting us know that studies are useful, but it seems like once you find out the information of how much you need to take, you're through with the bottle.

And I'm concerned that without having that information, every four to six hours leads us into the toxicity range of acetaminophen, and that's the six grams if you do 100 grams every four hours. Should we embolden that?

I think it might be something to embolden so that at least if they're not interested in reading, they see there's something to pay attention.

Lastly, the issue of toxicity is addressed with liver damage. What does it say? Oh, yeah, "acetaminophen may cause liver damage." I think separating that from the alcohol warning is critical because the point that's been made in a very clear and very tragic way today is that alcohol is not the only risk factor. Toxicity can be related to dosing, and that's it.

So I think it would be more prudent to say

overdosage of acetaminophen can cause liver damage in a separate area from the alcohol warning so that we don't distract from those who are not drinkers, are not drinking three drinks a day and they say, well, this is just for those who are drinkers.

The last point has been made multiple times about font size. I think that it's crucial to have the font size so that you actually pay attention to the active ingredient on the front of the bottle, but as well, I notice in the active ingredient label which is really much improved because it's highlighted though, I have to hold the bottle over here to see that that active ingredient is actually -- thank you. I'm going to use those today.

(Laughter.)

DR. CLAPP: -- is actually acetaminophen.

And so although the active ingredient is labeled, it's not emboldened, and so it's interesting to see the highlight, but I think embolding it will help us who are over 40.

Thank you.

CHAIRMAN CANTILENA: Thank you.

Dr. Katz.

DR. KATZ: Thank you.

I also agree with much that's been said,

but at the risk of being repetitious, I'd like to be very specific so that the record is clear.

Number one, I would reiterate that all ingredients need to be on the front, including on the combination products and including the concentration per dose. For example, it should say acetaminophen, 500 milligrams per tablet, or phenylpropanolamine, X milligrams per tablet, as opposed to just acetaminophen, and then you have to dig in the back to find out how much it has.

Number two, I think that the class should also be in the front. So it should say acetaminophen, pain reliever; phenylpropanolamine, decongestant, and then the amount, all in the front.

Number four is that it has to be on the bottle itself, not just on the box because everyone throws their boxes always, as has been pointed out already, and nobody can remember anything until they actually have to go to the bottle and take what's in it.

I was sitting in the airport on the way here, and a guy was giving one of his friends some Aleve from a bottle of Aleve that he had and was telling him, "Yeah, my doctor told me that you're not supposed to take that with something else, but I can't

remember now what he said and what a great doctor I have for telling me that."

And you know, if it's not on the bottles, you can refresh your memory every time, you know, whatever the issue is. Then you can pretend that it has never been mentioned.

Then I agree with having a warning on the bottle that there are other products that also contain acetaminophen and that you need to only combine them with a doctor's supervision. And I agree with there being the specific mention of liver damage as the potential consequence.

The issues of dosing under age two have to be dealt with right away, and again, I was happy to hear Byron suggest earlier that the same things need to happen with prescription combination products that contain acetaminophen. What's good for the goose is good for the gander. Otherwise, you know, we're not really accomplishing our objectives.

I would argue against any kind of black box or Surgeon General's type of warning that says that can cause liver damage or something because I feel that that would cause more harm than good from a public health standpoint.

And I would also recommend that while I

think all of these things should be done right now, there should also be implemented immediately a period of study with specific mentions of what exactly needs to be studied with regard to consumer behavior such that this can be an iterative process since, as has been pointed out, we really don't know exactly how these changes will impact on consumer behavior.

And that period of study and revision needs to be incorporated as part of the plan.

In terms of the dosing by weight issue, you know, I share the concerns that the dosagings are very confusing and inconsistent. I would recommend that those issues be sorted out during that period of study that follows implementation of label changes because I feel that those are thorny issues; that if one had to make those decisions now before implementing changes, those changes may never get implemented.

CHAIRMAN CANTILENA: Thank you.

Dr. Johnson.

DR. JOHNSON: I vote in favor of changes and, again, will be a little bit reiterative. I think that a liver warning should be added, and it should clearly be separate from the alcohol warning.

For drugs that are presented in blister

packs, nd one of the examples that went around was, I think that's usually going to be combination products. I have a concern that people throw away the box even in the blister packs, although maybe less often than with bottled drugs, and often the blister packs have almost no information on them.

And so I think it's important as the example is shown there that it does say "contains acetaminophen," at a minimum, and preferably would have all of the drug names, not just the brand name of the product."

For combination drugs, I think that it's actually quite unacceptable that the rules are different and that the drug names don't have to appear on the front, and I applaud McNeil for their efforts to change that, and the examples provided has a statement, "This product contains X number of drugs," and I think most consumers have no idea how many drugs are in those combination products, and then lists those all by name.

And I think that that's something that should be considered as a requirement as opposed to a voluntary step.

I think the prescription acetaminophen containing products are also important, and I think

auxiliary labeling for Rx products is going to be really critical to getting the message across in a sort of complete way, and therefore, education of pharmacists who are the ones who have to stick those labels on the prescription bottles is going to be really critical.

In terms of the warning, I think that it's important that the message is not just overdose and instead says "exceeding the recommended dose" because, again, if you say overdose, then people who aren't attempting suicide will assume that that doesn't apply to them.

And so it has to be very clear either that it's both overdose and exceeding recommended dose or just exceeding recommended dose.

And then finally, I think that we all sort of have to admit that the information on the product probably doesn't do as much to educate consumers as we'd like, and so I think particularly TV advertisements is probably really the way to educate.

And a couple of months ago I saw the NCPIE advertisement about my drug has two products, and I was really impressed. And I will admit I'm probably not the average consumer in this regard, but I found it to be a very, very effective commercial.

And I think if people saw that kind of commercial, it wasn't focused on any specific product, but it gets a very, very important message. And so I think that kind of approach is very important, and I think all of industry who has these kind of products should support such efforts.

CHAIRMAN CANTILENA: Thank you.

Dr. Williams.

DR. WILLIAMS: I'll defer.

CHAIRMAN CANTILENA: We'll come back to Dr. Williams.

Dr. Uden.

DR. UDEN: The other Dr. Williams has left us.

I agree that we --

CHAIRMAN CANTILENA: How do you mean?

DR. UDEN: I have his chair. That's all I know. I don't have to worry about my wheels falling off anymore.

I agree with voting that you have to have label changes immediately. I remember back in the early '80s when I was managing many Tylenol overdoses in pediatric patients and knew the literature very well to read -- and I've been out of that gig for a while -- but to read that the unintentional overdoses

could occur at median doses of around five to six grams a day was very surprising to me.

Therefore, I agree with everything that's been said, that the names have to be on the front with the concentration of the drug.

And I also am a very big fan of label comprehension studies, which are multi-cultural, multi-literacy that would go along with this because I don't think this OTC product has been -- that that has happened with this.

CHAIRMAN CANTILENA: Thank you.

Dr. Williams.

DR. HENRY WILLIAMS: I agree with the previously stated package labeling, as well as the concerns about the various overdosing, as well as the utilization of the alcohol warning as separate from the liver warning.

The concern that I have is a little bit on the other side of the consumer. The concern that I have is associated with the labeling. It says stop taking; ask your doctor.

The question I have is whether or not our doctors are informed with the proper information about the product and whether or not we as individuals in education should propose that this also have a health

care educational -- health professional education component to it, as well as the consumer education.

I hate to have a patient come to a doctor's office who has not been sophisticated in the knowledge about the Tylenol risk and not being able to identify it or even able to attribute other satisfactory marks to it.

So mine is education plus the yes.

CHAIRMAN CANTILENA: Okay. So your vote was that changes should be now.

DR. HENRY WILLIAMS: Right.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Neill.

DR. NEILL: Yes, changes now. Put the name on the front of the pack. Prescription drug should be subject to this as well.

The only substantive addition that I'd want to make has to do with the concentrations. In counting up the dosage forms for acetaminophen available, I count eight, which include within them 24 different concentrations or strengths.

The majority of that variation occurs in the pediatric forms. Some of those are so close together as to be meaningless. And while it's true the most commonly found strengths over the counter are

going to be 100 milligrams per mL for the dropper, which isn't expressed that way; it's expressed as 80 per .8 because the dropper is .8. I don't know why, but it is.

And then there are solutions and liquids for older children which vary in concentration, but can be had when expressed in the same per milliliter concentration as the drops are in your 12 milligrams per milliliter, 24, 32, 33.3, 33.4, 65 milligrams per mL. There's a 48 milligram per mL as well.

Why all of those are available, why they are -- and I had to do a lot of calculations to put those all in a common denominator because some are expressed in per 15 mL. Some are -- which is a tablespoon -- some are expressed as per teaspoon, which is five mLs.

I would have to remember that as a doctor, which I don't, and I've been doing this for 20 years now, why I would have to convert from .8 into mLs or mLs to five mLs or to 15 mLs is just beyond me. And you know, if I can be confused, anybody is going to be confused.

The fact that I cannot reliably tell a parent over the phone, "Go in for your six kilogram child and give ten milligrams per kilogram," and know

what dosage form they are going to find in the shelf makes it impossible for me over the phone to give a useful recommendation.

I may say, "Go and get X brand," but if that costs twice as much and there's a concentration which is similar, there's no good reason not to use the other, but there are five different forms that are there.

So we need to reduce that variation in what the consumer sees on the shelf and what I have to try and remember in the middle of the night.

CHAIRMAN CANTILENA: Dr. Patten.

DR. PATTEN: I will support making changes immediately. I certainly think that all active ingredients should be listed on the front of the label, the label of the package, and it should be on the label on the actual container, including on the back side of the bubble packs.

I think that the size of the letters of the ingredients becomes an issue. It needs to be easy for people to read, and I noticed something in one of the packages going around, a very subtle kind of a thing. It's the package that does list the ingredients on the front, but it first lists the category and I think maybe that's it in cobalt blue,

and then you get an arrow that takes you to acetaminophen in a pale orange against a pale yellow background.

And the human eye will be drawn to the cobalt blue and perhaps will go no further. I think there's a good body of literature probably coming out of the discipline of psychology taking a look at color and the way the human eye works and is drawn. And I think maybe that there should be greater attention paid to that so that the consumer will pay as much attention to the active ingredient listed on the front of that label as to the category that the ingredient addresses.

Another question I would ask, we see here in the Drug Facts over and over "do not exceed" such-and-such a dose. "Do not exceed," "do not exceed." And I'm just wondering why instead the label doesn't say, "Do not take more than."

I think "exceed" is not a word that everyone uses as part of their common vocabulary, but if you tell people not to take more than so many tablets in a given period, it might be more useful.

And then since my job is to represent consumers, I'll just remind everyone that not every consumer of OTC drugs has a doctor or has access to a

doctor, and I'm not sure how labels can address that problem, but certainly when all labels say "or ask a doctor," "see a doctor," "ask a doctor before this, that or the other," we have to take into consideration all of those folks in this country that don't have access to a doctor.

CHAIRMAN CANTILENA: Thank you.

Dr. Wood.

DR. WOOD: Well, I always worry about these signs at the side of the road that say "beware of falling rocks," you know. I'm never quite sure what to about that.

(Laughter.)

CHAIRMAN CANTILENA: You're supposed to drive faster, Al.

DR. WOOD: Right. You know, or when you pull down the thing on your SUV and it says, "This SUV may roll over." You know, I'm not sure that makes me feel much safer.

But seriously, I think there is a need for labeling changes right now, and I think most of it has been covered. We should have a stick on label for Rx preparations that looks the same. Somebody said they should all be in the same color.

I think we should also though, given what

we've all articulated about our concerns about lack of data go further than that, and I don't see why the agency shouldn't, along with the manufacturer set a target for risk reduction.

Why don't we set a target that says the number of overdoses from acetaminophen should fall by a certain percentage by a certain period of time, and that will encourage everybody to come up with a plan that reduces risk.

I mean, you know, just think of the Resulin experience. We went through all sorts of attempts to reduce the hepatotoxicity produced by that, and they were not notably successful, and we were only addressing physicians with that.

So I would like us to go further than just, you know, putting up signs that say "beware of falling rocks" and encourage the agency to come up with a risk reduction plan with the manufacturer that is testable and that demonstrates some sort of results within some period of time. And if the first situation doesn't work, then get back to the drawing board and do it again, guys.

But we certainly have better data here on the number of people who are getting hepatic failure from overdoses from acetaminophen than we've probably

had with any other risk that we've dealt with in prescription drugs certainly, and we ought to be able to reduce this number lickety split.

And the fact that we've gone on for 25 years just kind of dickering around, putting out more road signs doesn't seem to me a very satisfactory outcome.

CHAIRMAN CANTILENA: Thank you.

Dr. Day.

DR. DAY: Well, I'm in favor of labor changes now, especially about dosing, and I'm not so concerned about getting these things on. I think we're going to vote for them, but I'm very concerned about how we put them on.

Yes, we can increase legibility and font size. Those are very standard, human factors, principles that are well known, and we can rely on those.

Yes, we can enhance readability so the frequency of words in the language and the sentence length or the bullet length can be adjusted. We know about that.

However, we can do all of that and the information still may not be cognitively accessible, and what I mean by that is the ease with which people

can find, understand, remember, and use the information. People on this side of the table have already pulled out one good example of how it might not work in some cases by subsuming the liver damage under the alcohol warning.

So the principle there is chunking. You've got to chunk together different types of information and separate it out from information it doesn't go with, and so I'm very in favor a big supporter of the Drug Facts format. However, it gets to be a bit repetitive, and I'm not sure that it will enable us to enhance some of the messages we want to enhance unless we think outside of this box. It's a wonderful box, but think outside of it for a moment and consider another cognitive principle, and that is if you have the same information in two ways, that increases the chances that people are going to get it.

And two effective ways are text and pictorial, and I've made a little pictorial diagram of dosing. So it's sort of a thermometer type thing, and you can have number of tablets per unit of time going up like this, and you have kids here, adults here, and a big cross-out here that says you never take that much, and so on.

So whether it's this pictogram or some

other pictogram, having both a linguistic and a pictorial representation of the same information could be to the advantage of the consumers.

Now, I know that industry will sometimes come back and say, "Well, but you know," and then you have to have these other pictograms. If you enhance one part and then the other part might fall away and so on and so forth.

So instead of having to put something out, try it and see what happens, we develop alternative representations for the same information now, test them quickly in a laboratory situation in a labeled comprehension study where you test for multiple cognitive processes, such as finding, understanding, remembering, and using; see which ones win; see if they work across different populations with different literacy skills so that people who don't read might understand the pictogram or people with multiple language backgrounds. All of this can be found out in the order of months.

This could be a study within one month, a set of them within six months, and so then we know how to do it.

So I hope that today as we vote for things to be on the label, that we will take into account

that we really need to think hard and develop alternative ways to do that and test them before they then go out into the real world, and we can do actual use tests as well once the laboratory tests are completed.

One final comment, and that's for the prescription medications. It's great to have the pharmacist put on the auxiliary label. We've done research where we have the same patient, same drug, same pharmacy, having gotten refills five or six times. Every single time there's different labels on there.

DR. COHEN: Just let me just comment on that because you can standardize very easily the way those labels are printed out if it's in the computer system itself. In some of the pharmacies the chains are already doing that.

So if you're using a combination ingredient, it automatically will print out on the label in a standard way. So I just wanted to mention that.

I would definitely vote yes. I think that the label changes are needed immediately on the packages. I think it's really important that FDA spend a little time looking at the best way to do

this.

I think there needs to be a standardization. There needs to be a standard font size. There might need to be a standard background, as I said, to call out that information. You might need to use all upper case text or something like that. I don't know exactly the best way to go here, but it certainly can make a difference, and we've seen that with some other products recently where contrast was given. So that's important that it be done and it be done in a standard way.

As I said earlier, and I agree with my colleague down at the other end of the table about the statement "call your doctor," it's just not enough. It should also say "call your pharmacist," as many of the other products do that are over the counter now.

And I realize that some of these drugs are only available in supermarkets and that's where they're purchased, but if people need guidance and they need it in a hurry, the pharmacists are readily accessible, and I know they're willing to help.

That said, I have to agree with Julie Johnson. We do need to educate the health care practitioners. They are not all as cognizant as they should be of the appropriate dosing.

I mentioned earlier the term droppers full being confused, and I think that needs to be addressed with the dosing if we're going to have the concentrated form with the dropper. Whether it's a color line or some other mechanism, that needs to be addressed.

The idea of the safety lock, and they showed some evidence of its effectiveness with the infant's concentrate Tylenol product, that not being available with other manufacturers or with other products, I know that this manufacturer McNeil does have a cough and cold product. It's not available now, but they explained in our packet that it's because it's not available in a suspension form. And it was my understanding they might be reformulating it so that it's in a suspension form.

That's great, but I think any highly concentrated form should be available in that packaging, and I think that should be part of it.

And then finally, again, I think this is -- I'm sorry to repeat, but this idea of expressing the concentration of the liquid formulations on a volumetric basis rather than a metric weight basis is important per mL or whatever the standard is so that you would be able to compare 32 milligram versus 100

milligram per milliliter, for example.

We've had health professionals -- at least one case I remember that was reported to us -- where an RN actually used the concentrated liquid in a teaspoonful amount because of confusion with the amount of drug in there. So I think that's important as well.

Thank you.

CHAIRMAN CANTILENA: Okay. Thank you.

And I vote yes for now, changes, and I will not, you know, reiterate a lot of the things that have been said. I would like to compliment, you know, McNeil on this new packaging. I think it's an excellent first step and all of the comments that were made to improve I think, you know, should be considered, but I think certainly an excellent first step. That is very good.

Just one other thing to emphasize. If at all possible, standardize the concentrations in an age group so that you don't have all of these, you know, concentrations which are very confusing.

In my own household we have at least four different concentrations, and I have to use a calculator when I dose my kid. Fortunately she doesn't get sick that often. So good for her.

Anyway, Dr. Jenkins, I think, has a comment about, you know, dosing, or Dr. Ganley.

DR. GANLEY: Yeah. I think it's worthwhile for us to just make some comments on one of the issues as has been raised regarding the citizens' petition to include dosing for children under two years of age.

We've been working on this petition for the last two and a half years or so, and it's not as straightforward as people think, and originally the petition has to go down to two months of age, and after we research the literature and prescribing practices and such, it turns out there's a significant amount of bacteremia and serious infections in a population of children with fever from two to six months of age.

And so that was one of the issues that we had to address, and you know, again, that's based on our going out and collecting that information.

The other thing is that the proposal was to base it on weight or the dosing on weight or age, and it turns out that the charts that would have been proposed in that, there's no correlation and weight. And we actually went to the CDC age-weight tables, and it's very difficult to dose by age in that age group

because the children are growing so quickly.

And so those have been some of the things that we've been struggling with. There is actually a proposed rule written that's going through endorsement clearance, and we've actually incorporated some of the comments that you already have made, such as standardized concentrations and prominent labeling to distinguish concentrated drops from the suspension, and actually possibly a measuring device that would be included to that product, for that product.

Because, you know, when you think about, well, we just put the dose on it, and whether it's teaspoonsful or whatever, well, a teaspoon is not a standard measurement in a lot of people's houses, and so when you start thinking about these things and think, well, we'll just put the correct information on and everything will be fine, we already know today, well, everything isn't fine if you think you have the correct information on products for people over two years of age.

And so it's a much more complex issue, and we actually are asking for information to support, you know, what the wording should say so that, you know, we get it right for the population of six months to two years of age.

But I think it's important to understand that, you know, we've struggled with trying to get this rulemaking correct, and there's a lot of issues in it, and it's just not as straightforward as folks think. But it is a priority to get done.

CHAIRMAN CANTILENA: Okay. Thank you.

What I'd like to move to now is the issue of drug interactions and, you know, disease states having an influence on, you know, the risk of acetaminophen usage, and I'd like to use the same format. I think the last two issues can be dealt with a lot faster, but I think I would like to hear everyone's comments on this particular one.

So we'll start on the other side of the table, and really the question here as I've formulated it: is there sufficient information to make label changes concerning drug-drug interactions or, you know, disease states, you know, malnutrition, et cetera, et cetera that we talked about earlier at this time?

And if the answer is yes, if you would sort of specify, you know, what you're comfortable with in terms of adding at this point, you know, to the label and what you feel we have to have, you know, further information on, so further study.

So again, we're just specifically focusing on drug-drug interaction or, you know, disease states and whether or not we should alter the label to include, you know, warnings for those specifically, and if yes, what should be included in terms of what you're comfortable for; and if no, then if you can specify the kinds of studies that you think would help you get to that point, if ever.

And so if we can start actually with Dr. Cohen, then we'll go around this way.

DR. COHEN: I'm going to pass on that for now.

CHAIRMAN CANTILENA: Okay. Took you by surprise.

Dr. Day.

DR. DAY: I would favor having something on for drug-drug interactions, for what our current state of knowledge is about that. For the subpopulations, I think they vary across the ones that we've considered from people with compromised livers to malnutrition and so on, and I haven't heard much data today about malnutrition and so forth. So I think that that's a varied category, and I think we should hear from everybody across those different subpopulations.

CHAIRMAN CANTILENA: Okay. Dr. Wood.

DR. WOOD: Well, I guess the decision is already made with alcohol. So we should -- I certainly don't think we should remove that if that's the question.

In regards to the others, I'm not sure that we have data to support labeling changes at this stage, and I think that would have to be deferred until people had a better understanding of what induces 2E1, and in terms of malnutrition, while intuitively it might appear reasonable, I don't think there are data that give us a sense of whether the person who's dieting to lose, you know, weight to get into their bathing suit is at risk versus somebody who has got some cachectic state.

So I don't think we can make labeling changes that will be helpful to people at this stage.

CHAIRMAN CANTILENA: All right. How about on the issue of drug-drug interactions, you know, enzyme induction?

DR. WOOD: Well, the original Matthew chart that was shown early on actually said you should treat people with the antidote if they were on enzyme inducers, anti-convulsants specifically, at a lower acetaminophen concentration.

Bearing in mind that we're talking about consumer labeling here, that seems to me to be going beyond what we could reasonably expect people to deal with, and so I wouldn't advocate that at this stage, except that as knowledge becomes available, that might change dramatically.

CHAIRMAN CANTILENA: Okay. Dr. Patten.

DR. PATTEN: The decision is made with regard to alcohol, and I'm wondering. When you talk about drug-drug, are you also including the acetaminophen-acetaminophen?

CHAIRMAN CANTILENA: No.

DR. PATTEN: All right. Then I feel that I must defer to the physicians in the group with regard to a position on drug-drug interaction.

With regard to malnutrition, I agree with Dr. Wood. We heard very little. I'm assuming that that is certainly one concern regarding people who are addicted to alcohol, the malnutrition of alcohol.

A question that comes to mind, given that between five and ten percent of teenage girls and young women are involved in anorexia or anorectic type behavior, I just raise the question if there is any kind of a research database regarding liver toxicity and acetaminophen use in that particular

subpopulation. I don't know the answer.

CHAIRMAN CANTILENA: Thank you.

Dr. Neill.

DR. NEILL: No, I don't think that we've heard sufficient data to suggest a need for label changes, and that, in turn, I think, creates an impetus to make recommendations about so how do we get the data, and you know, the two most compelling sources to me today came from Dr. Lee and from Dr. Erush, and I think that to the extent that every time we have one of these meetings one of the questions involves what studies do you want; how could they be done; I think some additional thought needs to be put into that.

Both Dr. Lee and Dr. Erush are, you know, giving us data that comes from patients presenting to hospitals, and we've already heard how the poison control data is perhaps over representative of a different type of population. Somebody smarter than me needs to think about how to improve the surveillance that occurs to look for specific types of either drug-drug or condition specific factors that would help guide labeling if that's what we want to look at.

CHAIRMAN CANTILENA: Dr. Williams.

DR. WILLIAMS: I don't think we've had the information that we really need to put that label on, especially with the anti-seizure medications and the other medications that have caused reaction.

I think we do need the studies to specifically demonstrate whether or not there is a dose relationship and whether or not the indication should be placed there. So I'd defer until studies are brought back.

CHAIRMAN CANTILENA: Thank you.

Dr. Uden.

DR. UDEN: I agree. Don't have enough information.

CHAIRMAN CANTILENA: Dr. Johnson.

DR. JOHNSON: Agree that there's not enough information, and I think particularly for drug-drug interactions there's no compelling evidence, and I think even from a theoretical perspective you'd be a little hard pressed to come up with really convincing drugs that would be likely to interact.

CHAIRMAN CANTILENA: Dr. Katz.

DR. KATZ: In terms of the malnutrition fasting, I agree that we're not really heard enough consistent data to put any specific warning about that, nor is it clear to me how one would actually

define that in a consumer label.

And with the liver disease, I think it's the same, that we have not really heard consistent information yet that states that if somebody has whatever kind of liver disease that they're at increased risk.

And we have data from Dr. Koff and his experience and his consortium that may mitigate to the contrary, although I think that that data could be formally analyzed and it would be more persuasive that way.

In terms of drug-drug interactions, I would also defer to people who know more about that than I do. The one that I've read about that I would put forth to the committee for discussion, is that I've read that in some patients, acetaminophen can increase coumidin effect and increase prothrombin times.

I would ask people more knowledgeable than myself on the committee, you know, how significant a factor that is, but that's certainly in the pain management literature for both acute and chronic pain management.

In terms of what studies could be done to help clarify these issues as we go forward, to me it

seems clear that the next step beyond the K series, which is what we have now, would be a simple case control study of trying to identify, you know, whether and to what extent acetaminophen is associated with acute liver failure or hepatotoxicity and what other factors either combined with that or separately are also associated and then maybe causally related with hepatotoxicity.

CHAIRMAN CANTILENA: Thank you.

Dr. Clapp.

DR. CLAPP: No, for the general reasons previously stated.

CHAIRMAN CANTILENA: Dr. Alfano.

DR. ALFANO: I've seen no compelling information here today that would warrant the change at this time in this area.

CHAIRMAN CANTILENA: Dr. D'Agostino?

DR. D'AGOSTINO: I don't see any compelling evidence also.

I think in terms of the studies, I mean, things like surveillance and some of the cohort studies that exist, there are ways of getting a hold of the population in terms of the use of these particular drugs as opposed to doing it as a spontaneous reporting. Case controls and case control

studies and so forth I think are a real possibility and should seriously be considered.

CHAIRMAN CANTILENA: Dr. Laine.

DR. LAINE: I would agree no because there is a lack of information to support it.

I just would say that perhaps prospective observational studies from cohorts of hospitals, such as Dr. Lee was doing with acute liver failure, which could be sponsored by either governmental or industry groups would be very reasonable to quickly -- well, not quickly, but to attempt to just try to get all patients presenting to the hospital with acetaminophen overdoses would be very reasonable.

I'd just point out that flying here there was a 757 patient in one of our GI journals that looked at the effect of medications and outcome and actually suggested that opioids, for instance, were associated with a significantly worse outcome.

But if you had a large enough group of hospitals in the U.S. involved, I don't know whether HICUP (phonetic) or some of the other national databases do that now, but I would wonder if that's available now.

CHAIRMAN CANTILENA: Dr. Cryer.

DR. CRYER: Entirely agree with what's

previously been said. Not sufficient information to recommend additional risk categories, and these are areas, however, for definite future research for specific subpopulation evaluations.

CHAIRMAN CANTILENA: Dr. Lam.

DR. LAM: Based on the information that Dr. Slattery provided this morning, I don't think we at this point in time need to worry as much about SIP 1A2 and SIP 3A4, and I don't think we have enough information about SIP 2UM modulation to actually require some sort of a labeling change at this time.

CHAIRMAN CANTILENA: Dr. Davidoff.

DR. DAVIDOFF: Well, I would also agree that no is appropriate for now. I would suggest though that there might very well be additional information, important information to be found in areas that we haven't really heard much about.

For example, genetic studies. I mean, if people are getting into studying SNIPs now it seems to me it might be a very appropriate and important thing to look at in the people who appear to be unduly susceptible.

But that would be along with the notion of considering more seriously, as I mentioned earlier, a multi-factorial model. It may be that the mindset of

looking for Subgroup A and then Subgroup B, which is distinct, and then Subgroup C, each of them having a single risk factor, isn't really going to give us the answers, and I would think that the multi-risk factor model should be taken more seriously.

CHAIRMAN CANTILENA: Dr. Brass.

DR. BRASS: Since two colleagues mentioned the alcohol warning, I'm going to challenge that by asking where the number three drinks came from.

(Laughter.)

DR. BRASS: And are we warning -- does the three-drink warning mean anything other than -- so can anybody answer that question?

MS. LUMPKINS: Basically that three-drink number comes from the recommendations of the American Heart Association as to what constitutes sort of excessive alcohol use.

DR. BRASS: I was afraid of some answer like that because --

(Laughter.)

MS. LUMPKINS: That was what we had.

DR. BRASS: You know, the relevance of that definition to any risk, whether we believe there is one or not, you know, I'm uncomfortable. So, again, we don't have any data to change it, but I

think we should recognize that that is basically an arbitrary assessment and represents one of the areas of need for clarifying this.

I'm going to reluctantly agree that we don't have the data -- well, no, not reluctantly -- sadly agree that we don't have the data to change the labeling now, but based again on what we know about acetaminophen's mechanism of toxicity, I feel viscerally that there is a subgroup at risk, and we have not been able to identify it and, therefore, can't warn them. But I think that makes it a little bit more urgent in my mind that we work to define that population.

And I think there are three strategies that come to my mind. One has already been mentioned. I think that a careful surveillance network using standardized definitions, standardized collection techniques, unbiased event adjudication might allow a lot of information to be gathered very quickly about the populations we're talking about and provide objective information.

Two, I think we can challenge some of the hypotheses that have been put forth about risk factors and probe populations trying to identify those outliers that may be a theoretical risk. My own

concern again, as I've already alluded to, is that glutathione stores per body mass -- I mean per individual -- are going to vary a lot, and just again intuitively the petite female senior member of our society, not to be confused with the little old lady, clearly has less glutathione than the typical NFL football player.

And to say that therefore their risk threshold is identical just doesn't make sense to me. So I think that there are technologies that could be developed for noninvasively assessing glutathione stores, probing 2E1 distributions, et cetera, that might challenge some of the hypotheses and lead towards meaningful population subsets and obviously can be combined with genetic work.

And the third, which is related to our previous discussion, is I think we must understand fundamentally risk management strategies in the OTC population. We do not have any guidance how to do this.

I mean, this is the same thing in our X population, I realize, but we're talking about the OTC population, we're talking about problems of risk management without any database to assess relative efficacy of tools, effective interventions, et cetera,

and I think research in that area is desperately needed.

CHAIRMAN CANTILENA: Dr. Watkins.

DR. WATKINS: A couple of comments. First of all, I don't think it's been mentioned, but the NIDDK, National Institutes of Diabetes and -- Digestive Disease and Kidney -- is that what it is? Okay -- has put out a request for awards for a hepatotoxicity network that will be three to five clinical centers and a data coordinating center that I think maybe along with the acute liver failure network will provide an infrastructure to begin to analyze these questions.

And people have questioned whether it will be large enough and have enough influence, enough patience to be any good, but clearly with acetaminophen it will be good enough to get at, I think, a lot of the epidemiologic questions just because the issue is so prevalent.

In terms of drug interactions and risk of hepatotoxicity, clearly there is the ethanol issue. The difference over the last few years really is -- thanks to Dr. Slattery, there's a well worked out conceptual mechanism, even a mathematical model that can be used to simulate the extent of induction in P-

450 2E1 and production of the toxic metabolite as a function of blood level, of alcohol, and duration of exposure, and that was more or less validated in the short study I showed you one slide of that suggested drinking a typical bottle of wine over the course of an evening would increase your susceptibility, in effect, about 20 percent, 22 percent, statistically significant.

And although we'd all agree that's a very minor amount of increase in terms of susceptibility, the problem is the safety margin with the drug, as we've all heard today is quite, quite low. Even the data that we were shown by Dr. Dart, I assume funded by the company, suggested that somewhere in the range of ten grams per day, ten to 12 grams per day for three days, which is about two and a half to threefold the recommended doses, could cause irreversible liver injury in I think it was seven out of the 42 people.

So a 22 percent increase, on the one hand, doesn't look very substantial, but I think given the small exposure safety window, I think that has to be taken seriously. So I'm not sure where three drinks fits in exactly, but I think three stiff drinks might correlate with a bottle of wine.

And then the issue in terms of the

adequacy of that warning. Obviously if someone has a hangover at five in the morning and goes to their medicine cabinet, they're not going to call their doctor, and even if they did, it's not at all clear what that doctor or pharmacist would tell them I don't think.

And the recommendation we heard, I think, in 1998 was to actually have on the bottom reduced dosage, maximum 24-hour dosage, and that was rejected because there was no data.

There's still no, of course, good data on that, but again, Dr. Slattery's model does suggest the maximum induction you could get in this model, which I think corresponded to drinking somewhere around 70 bottles of wine over a two-week period, was about a twofold increase.

So at least theoretically there would be a reason to consider adding to that warning a reduction now. There's at least some theoretical basis to reduce that, I think, possibly to two grams in that situation.

Now, in terms of other drug interactions, there's a lot of anecdotal data that anti-seizure drugs can increase susceptibility to toxicity. We heard from Dr. Slattery though that the studies he's

done has not supported that, and the qualification being these were small doses, 500 milligrams of acetaminophen, not much larger doses where some of the other P-450s, like 3A4, might pick up the slack and begin to work.

But I would agree there's insufficient data to suggest a warning for, say, anti-seizure drugs or other inducers right now. These studies that have attempted to look at this carefully show that there is probably an increase in clearance through the NAPQI, the reactive metabolite, but it's offset by increased clearance through Phase 2 conjugation.

So the total amount that's produced is less, leading to the speculation that maybe the effect of the drug wears off more quickly, making people tend to take more than the recommended dose, in which case you could then postulate a mechanism for increasing the total amount of NAPQI.

But at least right now I don't think there's any evidence or enough evidence to suggest a warning for other inducers.

The only other drug that induces P-450 2E1 is isoniazid. There have been a handful of cases of patients taking isoniazid who have gotten acetaminophen liver injury apparently at doses less

than 15 grams in a 24-hour period.

However, again, thanks to the work of Dr. Slattery, patients receiving isoniazid actually have reduced 2E1 activity because of the substrate inhibitor interaction. So you would have to postulate they would be risk only when they stop taking isoniazid, and again, it gets confusing, and I think right now there wouldn't be enough evidence to put a warning for isoniazid treatment.

Now, the other two areas are starvation. That certainly looked promising, and some of the initial association studies that came out, but more recently that's not seeming to be a constant theme in terms of susceptibility, and at least one study, Steve Shanker, the Spieg (phonetic) study where they looked at moderate caloric restriction in obese individuals sufficient to lose six pounds over a week, but not go become ketotic. There was no evidence of altered metabolism or increase in NAPQI.

So I also think that would be premature at this stage to consider a warning for starvation or dieting.

And then finally, I don't think that although there was some apparently convincing data shown of association with preexisting liver disease,

that really runs in the face of all the experience that hepatologists have had with acetaminophen, where I think it's generally felt acetaminophen is the safest of the analgesics that can be used in liver disease, and that includes even very severe end stage liver disease awaiting liver transplantation, where I think most hepatologists would prefer acetaminophen in that situation, though they would reduce the dose probably to two grams maximum in a 24-hour period.

And I think it would be doing a disservice if anything out of this meeting went forward raising the possibility that people with preexisting liver disease should avoid acetaminophen until we get more data, perhaps through this network.

So I'll end there and pass the mic.

CHAIRMAN CANTILENA: Actually I just have a follow-up, if I may, Dr. Watkins. If you were to or if a sponsor were to in an experiment with humans show a comparable level of 2E1 induction to the high risk period of alcohol, would you consider that a valid surrogate for, you know, higher risk of a drug-drug interaction?

So if you did a drug-drug interaction with Compound X and you were able to quantitate the induction of 2E1 and you were able to get it at the

same level as the vulnerable -- you know, in a period with alcohol, would that be in your mind sufficient to allow us to have that as a drug-drug interaction on the label?

DR. WATKINS: I don't think that would be enough in and of itself, just that observation, simply because the statement was made that whenever anybody asked about anything else, that always comes back to 2E1, and that's simply because we know the most about it. I think susceptibility is also obviously related to glutathione stores and probably only mitochondrial glutathione and other integrity issues in the liver.

And just that observation, I would be cautious without some sort of other data, epidemiologic, to jump to the conclusion that there was a risk.

CHAIRMAN CANTILENA: Okay. Thank you very much.

Dr. Wood, a comment on that?

DR. WOOD: Yeah. Paul, I'm not sure I would agree. It would depend on the data. I mean, I think if you had evidence of 2E1 induction and you also had evidence that the same drug induced hepatotoxicity with acetaminophen in animal model, which would be, you know, an afternoon's work so that

it wouldn't be unlikely that you'd have that, I would certainly if I was about to take both drugs -- that would give me pause, and I guess that's all you're trying to do in a label.

So it's hard to know how much further you could get than that. If you had animal data to support it, which would be easy to get, and you had evidence that you induced the pathway and produced increased amounts of the mercaptopurine in the urine, that would be worrying to me at least.

DR. WATKINS: Well, I agree with that. I think part of the question was though if the magnitude of induction was comparable to what had been seen with ethanol, which is 22 percent. So we're talking about a minor difference which I'm willing to accept as important because of additional clinical data that we have. It makes sense.

DR. WOOD: Right.

DR. WATKINS: As an isolated observation for such a small induction, I think that would be a cause to really go after some clinical correlate or some additional data. I'm not sure that would be enough to jump to a change in the label because, after all, ethanol probably is doing other things, too, such as influencing glutathione stores.

But it's a debatable issue. No question.

CHAIRMAN CANTILENA: Okay. Very good.

Dr. Elashoff.

DR. ELASHOFF: I have two comments. Although most of the data we have on risk factors or drug interactions is not very good, still I think especially since we're interested in the possibility of multi-factors, it might be worth doing some real in depth statistical analysis of what's there, although that's not awfully likely to be really useful. It's a lot cheaper than new studies and may give some hints as to what ought to be done.

The second is if now or in the future some specific drug interaction or state like the fasting state looks like it might be of concern, I think we should not just say, "Well, somebody should do some research." I think we should put some teeth into that kind of recommendation, and that such studies should be properly powered to really figure out what might be going on and not just use a sample size that everybody else uses in that kind of study.

CHAIRMAN CANTILENA: So your vote at this time is no for the label. Okay.

Dr. Cush.

DR. CUSH: I have nothing further to add.

I also think that we need more studies and more education, and I would underscore or second the suggestion by Dr. Wood earlier about actually studying not only risk factors, but an actual plan for risk reduction.

CHAIRMAN CANTILENA: Dr. Crawford.

DR. CRAWFORD: I vote in concurrence with what everyone else has said, and there's no need to expand further because it's been so well articulated primarily, but also because I think it would be difficult for you to understand me through the chattering of my teeth.

(Laughter.)

CHAIRMAN CANTILENA: Dr. Furberg.

DR. FURBERG: At this time, no reason for change.

CHAIRMAN CANTILENA: Thank you.

I also vote no -- oh, I'm sorry. Yeah, go ahead, Dr. Cohen, and then I will.

DR. COHEN: I wanted to vote no, and the reason for that was adding yet more complexity to the label, and I wanted to, you know, have the benefit of the discussion to make sure, but I didn't hear anything either.

You know, we heard it before. Every time

you take a step forward it could be a step backward as well, and I think that was important to consider.

CHAIRMAN CANTILENA: Thank you.

And I also vote no for the reasons that have been articulated.

DR. DAY: Could I clarify?

CHAIRMAN CANTILENA: I'm sorry?

DR. DAY: Could I clarify my vote before when we were going around this way?

CHAIRMAN CANTILENA: Oh, Dr. Day. I'm sorry.

DR. DAY: I had said I voted yes for drug interactions. I was considering alcohol and the possibility of strengthening that. I did not include that other substances.

So given that it's been redefined in terms of the other substances, then my vote is no.

CHAIRMAN CANTILENA: Okay. Yes, thank you.

In fact, right after you, Dr. Wood asked a clarifying question, and it was not to include alcohol.

Okay. I think I have one more question that I think requires an individual comment, and then the rest is fairly easy. And the question for

individual comment -- and I guess we're starting over on this side with Dr. Furberg this time -- is regarding the total dose, total daily dose, and the question is: based on what you've heard and what you've understood and know, assuming equal efficacy is still maintained with a reduction in total daily dose, do you see a reason at this point; have you seen enough information that would allow you to recommend to FDA that they consider lowering the total daily dose of acetaminophen allowed to increase the margin of safety?

DR. KATZ: Just to be clear, that assumption is not correct.

CHAIRMAN CANTILENA: Well, the part that's complicated is if you recommend -- you really can't isolate safety, I mean, in the absence of lost efficacy because when you lose efficacy, you're probably going to use more, as has been suggested.

So I guess the question is trying to get at the issue of margin of safety, and I thought we would isolate it by the assumption.

If others have another way to ask the question which gets at should we increase the margin of safety --

DR. LAINE: Can I ask a question?

CHAIRMAN CANTILENA: -- I'm happy to hear that.

DR. LAINE: Can I ask a question? What you're saying is if it's just as effective at a lower dose? I mean, I don't understand. Why would anybody suggest using the higher dose if the lower dosage was just as effective in a drug in which we have some safety concerns?

I guess I'm not understanding the question.

CHAIRMAN CANTILENA: Yeah, actually that exists with other drugs, for example, because then, you know, your onset is shorter and you have an advantage for, you know, marketing.

DR. LAINE: Well, there's a difference in efficacy somehow then.

CHAIRMAN CANTILENA: You know, time to onset, we're sort of, you know, separating. I guess since we're here to advise FDA, I guess, should -- Dr. Ganley, would it be helpful for us to address the issue of total dose or would you rather not get advice in that area?

DR. GANLEY: Well, I think it was the way we had set it up originally was in the context of the subpopulations, and Dr. Watkins had pointed out, you

know, that he thought a lower dose for the people with chronic alcohol abuse would be appropriate.

Now, because when you think about it, you know, you have to -- and I'm presuming you're saying that because it will give you a wider margin of safety because we don't know if they're more sensitive to it, and it seems that there's a fair number of individuals in many of the -- you know, Dr. Lee's, and the AERs, and the University of Pennsylvania's, alcohol seemed to be a factor.

So if you're going to try to make it safer, and we don't know all of these other factors, you could lower and say that the total daily dose. The current recommendation to physicians now is just continue the four grams a day dose.

And if we think it's not an issue of, you know, the total four grams dose, and it's just that they're using too much, then we don't even need to point out chronic alcoholism. We just need to point out you just don't take too much. Okay?

But the issue is if they're a subpopulation that is at risk, okay, do you lower the total daily dose? And that's what I thought you were suggesting in your comments, is that they seem to be at risk, and it seems that a total daily dose of two

grams would be more appropriate because otherwise if it's just an issue that people are misusing this and using too much, well, it doesn't matter if you're a chronic alcoholic or you have any of these other factors. It's just using too much.

So that's sort of the rationale of, you know, getting into that discussion, and that's what I thought you were talking about, is that we don't really know what the answer is. These folks are more sensitive. There are going to be some outliers that actually four grams a day is going to be a problem, and we should just lower the total daily dose, and I think that's what we're sort of trying to get some sense of.

DR. BRASS: It seems having this discussion after our last round is very difficult. I mean, I really do understand the question, and it's not assuming equal efficacy. It's assuming that the safety no longer justifies that.

But we've just gone around the room and saying we don't know who that subgroup is, and so without knowing who the subgroup is, I don't know how to recommend who would get a lower dose. If I knew who the subgroup was, that's who I'd be concerned about, and, yes, I would try to keep the dose lower

than the proportionate reduction in their risk threshold, but without identifying the subgroup.

And now, the alcohol is there, but since we've agreed that -- well, I've agreed -- that the three-drink thing is completely arbitrary and has no quantitative risk, you know, association with it, but I kind of do think it's better than nothing, again, how to titrate beyond that --

DR. GANLEY: But what you're doing is, you know, we're deferring to physicians, but not giving them any information of guidance, and the only guidance that they're getting is from the manufacturers that are saying take four grams a day.

Well, that's what a regular person without any risk factors would take. Okay? So to me why do I even need an alcohol warning? I should just say, "Don't take more of this because it will cause some harm."

But if you believe that alcohol is a risk factor and that you want to -- you know, this issue of outliers, that some people may be more sensitive at four grams if they have alcohol disease --

DR. BRASS: Okay. So my answer to that would be so now we're talking about really professional education, not the label indication.

But I would say (a) I want the person who's drinking more than three drinks a day to talk to the physician whether or not they're taking acetaminophen or not.

So that if this is the mode for them to get to the physician, I'm very happy.

CHAIRMAN CANTILENA: You're never going to get an appointment.

(Laughter.)

DR. BRASS: You just -- well, no, I won't say that.

Two, there is a wide range of three drinks or more, and that a physician might use that to make a very comprehensive assessment of the risks to benefit in that kind of setting, again, using largely judgment because that physician won't have any more information than we have, but we'll integrate all of the information on an individual basis to make a recommendation.

And how they interpret the existing data in the context of an individual patient, I think, is a challenge, but is you know why they get the big bucks.

And so I think that in terms of removing that from an OTC sphere is not inconsistent with what was said about our lack of understanding of the magnitude of the risk or how to manage it in the OTC

setting.

CHAIRMAN CANTILENA: Okay. So I mean, how I was thinking about this is if we can just focus on the alcoholics or the person over three drinks a day. Would the committee favor or not reducing the total daily dose in that specific population?

That's probably a little bit more focused. Is that what you were thinking of, Dr. Ganley?

DR. GANLEY: Well, I think that gets back to, you know, what populations you think are at risk and if you think alcoholics are at risk, and you know, I don't disagree with what you said, Eric, but I don't think a lot of physicians out there know the data on alcohol and, you know, the interaction with acetaminophen.

And so we let them out there be floundering, and you know, we're not conveying information to them, and you know, the manufacturers are, and they're saying it's four grams a day. Well, that's what it says to give anyone.

And so I think that's what we're trying to get out here. Should we be, you know, saying that it should be lower than four grams a day in certain subpopulations?

CHAIRMAN CANTILENA: Okay. Well, how

about if we do this? The last question specifically, you know, excluded the alcohol as a drug-drug interaction. So let's just come back and ask the question whether or not the population consuming three or more alcoholic drinks every day should -- it should be included in the label that their total dose be less than four grams. And we're not going to come down to a number obviously, but just that, you know, the information here to ask a doctor is not sufficient to get to a safety zone, if you will, for over the counter.

That's sort of what's implied in answering in the affirmative that they should be labeled to have less than four grams. So I think that's a little bit more clear and can be done, I think, relatively quickly.

So, again, I'd like to start at this end, Dr. Furberg, and the question specifically is: should individuals, the subpopulation consuming three or more drinks per day, should their maximum allowable, you know, dose of acetaminophen be less than what's currently allowed for the rest of the population?

And yes or no, I think, is the way to go, and if you'd like to comment on it.

DR. KATZ: But just to be clear, are we

still talking about the consumer label that's on the bottle or are we talking about the actual -- you know, the PDR or are we talking about professional education? What are we now asking?

CHAIRMAN CANTILENA: I was actually talking about the Drug Facts. So the over-the-counter drugs.

Dr. Furberg.

DR. FURBERG: It would seem prudent to say yes.

CHAIRMAN CANTILENA: Okay. Dr. Crawford.

DR. CRAWFORD: Sorry. I have to vote no again for right now. I'm comfortable with the data that we've been presented, and I just think more information is needed.

CHAIRMAN CANTILENA: That's fine.

Dr. Cush.

DR. CUSH: I agree. I think more information is needed, and that's an issue that needs to be studied better before it goes into the label.

CHAIRMAN CANTILENA: Dr. Elashoff.

DR. ELASHOFF: I haven't personally seen enough information to convince me that the four grams a day as a recommended dose, especially given as 1,000 every six hours and then leaving you hanging for the

rest of the day, is based on any sensible, real efficacy studies.

For example, would you be better to take 500 milligrams every four hours to even out the duration rather than worrying only about onset? And I don't see any information on individual variability in what kind of doses people really ought to be taking.

So personally for the whole safety issue, totally ignoring subpopulations, I haven't seen enough real information to support the, quote, recommended dose, unquote.

CHAIRMAN CANTILENA: Dr. Watkins.

DR. WATKINS: One thing that was very helpful in getting all of the briefing documents was to understand the complexity of all the issues involved and the idea that things that seem logical aren't always the best in terms of long-term outcome and switching people from acetaminophen to other potentially more dangerous drugs.

So ignoring that for the time being, I think, and assuming that four grams can't be lowered and still be effective and useful in the general population because that would obviously be desirable to go to two grams in everybody and widen the margin from threefold to sixfold, it does make sense to me in

the one population that now I think everyone would agree is at increased risk to recommend on the label a lower dose.

Now, whether that's, you know, three grams or two grams is, I think, debatable, and what I would think would be to say do not take more than two grams in a 24 hour period without consulting your physician or perhaps pharmacist.

So that at least at five in the morning when someone is in their medicine cabinet, there's some direction that gets them going at least in relieving their pain.

But, again, I understand after reading all of this this is a complex issue, and sometimes the big picture is not the same as, you know, my view of it.

CHAIRMAN CANTILENA: Dr. Brass.

DR. BRASS: I remain a little bit confused because I think the current label says, "Do not use. Consult your physician," and I don't want to then say, "Do not use. Consult the physician, but if you insist, please use a lower dose." That doesn't make sense.

On the other hand, I'm sensitive to making sure of the public education because certainly, again, I would hope that if a person like this entered the

health care system, the care would be individualized and certainly on an individual basis using the least effective dose for that person.

So you would not start therapy with that person at four grams a day, and you wouldn't get the four grams a day without monitoring and considering the alternative therapies.

So I think my answer is -- I don't know what my answer is.

(Laughter.)

DR. BRASS: So is that a no or a yes? But that's my answer.

CHAIRMAN CANTILENA: Thank you, Dr. Brass. We'll come back when we figure out what you've said.

DR. JENKINS: Dr. Cantilena.

CHAIRMAN CANTILENA: Dr. Jenkins.

DR. JENKINS: I think it's important that we read what the alcohol warning actually says because I think Dr. Brass maybe didn't get it exactly right. What it says is, "Alcohol warning. If you consume three or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers. Acetaminophen may cause liver damage."

So it's not exactly that says, "Don't use

it."

DR. BRASS: Well, that may be one of those label comprehension things because I --

(Laughter.)

DR. BRASS: -- because I thought the intent of that was not to use it.

CHAIRMAN CANTILENA: Right.

DR. BRASS: Whether it conveyed that or not, I don't know, but I interpret the intent of that was not to use it.

DR. JENKINS: I think it can be interpreted by others that it's permissive, that you should talk to your doctor, but it does not say that you absolutely cannot use it.

DR. CUSH: But i also sounds permissive to using the drug as well.

DR. JENKINS: Yes.

DR. CUSH: Meaning using acetaminophen, which I think is sort of against the intent. I would think it would be.

DR. NEILL: As if our putting on the label "don't use" for an alcoholic who is told, "Don't drink." Why don't we just put, "Don't drink"?

(Laughter.)

CHAIRMAN CANTILENA: Well, that's the

subject of another meeting.

DR. NEILL: Yeah, but it makes it easier to answer.

CHAIRMAN CANTILENA: Right. I think that we've just enrolled the first two subjects in our comprehension study of the label.

Dr. Wood.

DR. WOOD: You know, I have great concern about us punting this to the physician. You know, I was just sitting here thinking of being in bed at five in the morning and the phone ringing from some drunken guy, you know, calling me up to ask me if he should take four Tylenol or two Tylenol, and I can imagine what I'd say, and it wouldn't wouldn't be thinking about 2E1 activity or whatever.

You know, I think the whole concept actually is flawed. I mean, it goes beyond this issue, and it goes back to this issue of risk reduction.

I think we are kidding ourselves if we think we're reducing the risk of a drug by telling a patient who's standing in a pharmacy or standing at their bathroom cabinet to call their physician, who has no concept of this.

You know, here we have spent days reading,

you know -- my Federal Express man practically died delivering this stuff.

(Laughter.)

DR. WOOD: And, you know, we've been through all of that, and you know, these great minds can't decide what to do, and yet we have utter confidence that we can say to patients, "Call your physician at five in the morning and he'll tell you exactly what to do."

That's nuts. So, I mean, I think we should back away from these warnings that make us all feel good, but in fact just defer the decision to someone else who is certainly not as well read on this as the people in this room.

So I think, you know, that makes me -- you know, I laughed about the rocks, you know, "beware of falling rocks," but we're in the same business here. So I think, first of all, I don't think we have data to say what we should do with the dose. That's the first thing, and to grab some number out of thin air certainly makes me very uncomfortable.

Somebody said already, you know, you ought not to drink, you ought not to smoke, and you ought not to drive your car too fast, and so on. But clearly coming up with some arbitrarily chosen number

plucked literally out of thin air has no possible basis, scientific basis, and nor does asking your doctor to do that at five in the morning, you know, in God knows where, Tennessee.

CHAIRMAN CANTILENA: Right, but the question is really for a lower dose and not a specific number, you know, just to clarify that part.

Dr. Davidoff.

DR. DAVIDOFF: Well, I have at least as much discomfort -- I would have -- saying either yes or no as those who have already spoken, but I guess if I had to tilt in one direction or the other, and statisticians are familiar with the notion of a trend as compared with a fairly clear-cut statistical significance, I think I would trend to actually including some indication of limiting the dose at least in people who drink a great deal.

That's I think probably just a sense of being conservative. After all, it seems the related question that kind of we started out with was how much analgesic efficacy would be lost by doing that, and I think it would probably be a moderate or modest amount would be lost.

So I think that the tradeoff seems reasonable to me from that point of view.

We've also heard that gastroenterologists at least anecdotally tend to limit the maximum dose of acetaminophen they use in their Hepatitis C patients when they're getting interferons, which kind of bolsters the sense that this trend might be not inappropriate.

On the other hand, we've heard that the French are raising the dose, the maximum dose. But that's France.

PARTICIPANT: That's up to the U.S. level.

DR. DAVIDOFF: Up to the U.S. level, but they're going in the opposite direction, in any event.

So I think if I had to say one thing or the other, I would probably say yes, but with a lot of caution.

CHAIRMAN CANTILENA: Dr. Lam.

DR. LAM: Based on what we know about the mechanism of toxicity, I would say theoretically yes, but practically I don't think we have enough information for me to say do it now.

CHAIRMAN CANTILENA: Dr. Cryer.

DR. CRYER: Yeah, I entirely concur. It's a very, very concerning issue. You know, when you look at Dr. Lee's database, there are 70 percent of the people who had failure were taking -- on

acetaminophen were taking four grams a day or less. And so, yes, we're concerned, and yes, intuitively we say there should be some lower dose to decrease the potential for toxicity, but we just don't have -- this is not a data driven decision, and we don't have sufficient information.

Additionally, in terms of how we uniformly apply this across acetaminophen containing products becomes more concerned, more problematic. What do you do with all of the prescribed products where there are acetaminophen combinations?

And you would have to also implement the standard across the prescribed products as well as the combination products. And so if the answer is yes and if the answer is yes at a certain quantity, then you're also going to have to have these discussions about how you do this across all of these products.

So for now, although concerning, I would say no.

CHAIRMAN CANTILENA: Dr. Laine?

DR. LAINE: I equally have angst about this. One of the things I was considering at least is under the alcohol warning saying something like acetaminophen may cause liver damage when taken as directed or when taken at full dose as directed, at

the full doses, because somehow get across the point it can happen, although I'm not sure it will really help that much compared to the typical alcohol warning.

So for that reason, although I considered that, I'm going to go down no.

CHAIRMAN CANTILENA: Dr. D'Agostino.

DR. D'AGOSTINO: I'm going to say no. If I recall the efficacy studies, and I remember reviewing them, there are a number of these. There is a difference between the dose level, and you drop the dose now and they get no effect. They start taking another pill to sort of catch up, and so forth. You do get yourself in a spin.

We just don't have the data at this point. No.

CHAIRMAN CANTILENA: Dr. Alfano.

DR. ALFANO: So I don't vote, but the alcoholic warning as it says "alcoholic warning," and I don't know about most of you, but I've been in social settings where over a dinner people have said, "I guess I'm having wine tonight. I have a headache, but I'm not going to take my Tylenol."

So it does have some impact. Admittedly that's not focused at the alcoholic, and I give

physicians a little more credit for being able to guide their patients not necessarily to a specific lower dose of two grams or three grams, but to use it wisely, to use it sparingly, which is typically what would play out.

So I don't think it's bad at all the way it currently exists.

CHAIRMAN CANTILENA: Dr. Clapp.

DR. CLAPP: Dr. Lam expressed my sentiments, and as well, I have concerns about the confusion with the dosing. If you're reducing it to two grams, are then we advising our patients who drink to take one 500 milligram every six hours, or are they going to take two every 12 or, you know, are we going to get more specific with a dosage that we expect will be efficacious in a patient who has alcoholic liver disease?

It's getting a little confusing.

CHAIRMAN CANTILENA: Dr. Katz.

DR. KATZ: I vote no for lowering the dose recommendations for that or any other particular subgroup for the reasons that everybody mentioned. The only one that I'll add is that what I think many of us are forgetting is there's a fair amount of interindividual variability in the dose response curve

to acetaminophen and all other analgesics, and there are a fair number of people out there who need higher doses than four grams a day of acetaminophen, and that's the right thing to do in those patients, and they do fine.

And the whole concept that I've heard mentioned a number of times today of acetaminophen having a narrow therapeutic window makes no sense to me whatsoever. I mean, given all of the exposures that are out there, if acetaminophen has a therapeutic window, what about all the other medications that we use? It clearly has the widest therapeutic window of any of our alternatives for analgesia. The only thing that has a bless of a -- has a wider therapeutic window is leave the patient suffering in pain.

So I personally think that we should not make dosage reductions, and I think that even in professional education we should also take pains to tell physicians that many patients have mainly to increase the dose beyond four grams a day.

CHAIRMAN CANTILENA: Dr. Johnson.

DR. JOHNSON: I would vote no for changes on several grounds. One, I agree with Dr. Brass that there's a certain amount of illogic in advising them something that suggests not to take it until they call

their physician, but then giving them a dose maximum if they're going to take it.

If we did want to do that though, I don't believe we have any data on which we would make a decision about what that dose maximum should be, and I think telling them to take less than four grams without a specific dose also provides no information because less than four grams is 3.99 grams. That is okay.

So I don't think that just saying less than four grams would provide information that would be valuable to anyone.

CHAIRMAN CANTILENA: Dr. Uden.

DR. UDEN: Sine apparently it's okay to have arbitrary information on a label, I think I've solved this. If you drink 12 drinks a day, it's one gram maximum; six drinks, it's three grams; three drinks, it's -- yeah, six drinks, it's two grams; three drinks, it's three grams; and if you drink one drink a day it's four grams.

I have to abstain from voting. I don't have enough information going from one to the other.

CHAIRMAN CANTILENA: Dr. Williams.

DR. HENRY WILLIAMS: Without the specific calculations I vote no also.

CHAIRMAN CANTILENA: Dr. Neill.

DR. NEILL: No.

CHAIRMAN CANTILENA: Dr. Patten.

DR. PATTEN: I would vote no, except I would also say that I think that the alcohol warning as stated here is a bit confusing. When it says, "As your doctor whether you should take acetaminophen or other pain relievers/fever reducers," that could be interpreted two different ways.

I have to ask my doctor whether I should take acetaminophen or whether I should take other pain relievers, or I should ask my doctor whether I should take acetaminophen or any other pain reliever.

In other words, are they all presenting the same potential risk as acetaminophen? So I suggest that the warning as stated be thought through a little more carefully even if we're not going to enter information on suggested lowered dose.

CHAIRMAN CANTILENA: Okay. Dr. Wood, do you have any further comments?

DR. WOOD: No.

CHAIRMAN CANTILENA: Dr. Day?

DR. DAY: I vote no, but I'd like to add some other reasons why, and that is if you put different dosing information up under warnings, then

you have dosing in two areas in the Drug Facts label, both in the warning section and the directions section, and you could get into the problem of the person at 5:00 a.m. in the medicine cabinet who's not an alcoholic pulls it out and sees that and takes that dosage.

I did want to inquire on other OTC labels are there different dosage levels for subpopulations, such as alcoholics, and if so, what's been the experience with that? Do we have any evidence?

CHAIRMAN CANTILENA: The only one that I'm aware of is napersin over-the-counter in elderly has a different interval.

DR. DAY: Right. So we have it for age. So we'll have it for age across a number of situations, but not for populations, such as we've been talking about today.

CHAIRMAN CANTILENA: Not that I'm aware of.

Dr. Ganley, any?

Dr. Cohen?

DR. COHEN: No, not without more information, and I think the warning that's there currently, it's a pretty good signal of you need to do something with the dosing if you're drinking. So

without more information, I don't think so.

CHAIRMAN CANTILENA: Okay. A comment from Dr. Neill?

DR. NEILL: Just a comment about categorization as an alcoholic. My understanding is that patients ought to -- in order to choose a medicine for OTC use -- ought to be able to self -- recognize the condition that they're treating and self-select, and I'm unaware that patients that I may diagnose with alcoholism can self-select.

So regardless of how we vote, within the real world of FDA deciding about the applicability of the label, simply putting it on the label won't allow patients to self-select in that way.

CHAIRMAN CANTILENA: Okay, and I also vote no for the reasons stated, but I share Dr. Wood's, you know, concern with the alcohol warning label and its ultimate effect and outcome.

Okay. To expedite things, let me just say when we turn our attention to what was discussion point number three with the combinations, does anyone not agree with the recommendation that any information in terms of ingredient identification should be also in the Rx combos clearly for the consumer? Is there anyone who feels otherwise?

Okay. Very good. So everything that we said about that will apply to the Rx combos in terms of total dose and recognition of ingredients.

The other area that I wanted to touch on briefly, and we could just do this very quickly, to advise the FTC and get comments from the members concerning things that they think should be included in direct to consumer advertising sort of in the spirit of, you know, the fair balance statements that occur at the end of the Rx DTC.

Is there anything specific that you would like to be included in that to warn, you know, patients?

We'll just open it up so that we don't go around the table again. Dr. Cush.

DR. CUSH: Not that I would want anything additionally included. I think the content of what's been said should just basically fall under the same directives regarding DTCA for prescribed products, and this should be overseen by the FDA and DDMAC and whoever ultimately might be appropriate.

CHAIRMAN CANTILENA: Any other comments on advertising, marketing for our FTC?

Dr. Cohen.

DR. COHEN: I know I mentioned it a couple

of times, but I really am concerned about the use of a brand name throughout a product line when there are different ingredients from one item to another to another, to another.

I think that's caused a great deal of confusion not just with consumers, but also with health care practitioners, and I think it would be worthwhile.

I know I've seen those ads, public service ads, that NCPIE was running as well, and I thought they were outstanding. That could be the subject of one of them.

CHAIRMAN CANTILENA: Dr. Wood.

DR. WOOD: I think there should be some warning of not to take whatever the product is being advertised with other acetaminophen containing products, and that should be explicit because that seems to be an obvious source of risk.

CHAIRMAN CANTILENA: Dr. Ganley?

DR. GANLEY: Can we just do making the assumption that FTC may not have the authority to make them do that? Okay? And so the issue here is one either of a legal issue or what you think the responsibility of the manufacturer is.

I mean, I think it's unfortunate that we

have to do everything by regulation here, and it's not based on what is the right thing to do or what's the wrong thing to do or somewhere in between. But I just don't think that we should just operate like that.

You know, if the FTC may not have any ability to make them do it, and so going around like this is not going to necessarily be very helpful. But I think the issue is, you know, what should companies do.

As I said, if they don't have the authority, it may require not just a regulation, but a law. Okay? So I think the issue is what would you like companies to do, and then we can translate that into something of whether it should require some regulation.

But to say that FTC should do this is not, I think, the approach to take. It's what do you think companies should do.

CHAIRMAN CANTILENA: Okay. So should we translate the comment then to a vote? You know, would that help in terms of, you know, as an action item from the Advisory Committee or --

DR. GANLEY: I think, you know, the issue is if you think -- you know, it gets between this issue of how do you educate consumers. Is it through

advertising or do you have different educational campaigns?

And so if you think it's through advertising, then you should be telling the companies, well, this is how we think you should be educating consumers also.

I think advertising is education for many consumers, and so I think that's really, you know, we're talking about consumer education and physician education, but one mechanism in education is the advertising.

So I think that's how it has -- if we're going to, you know, make comments on that, it's, you know, in the broad sense of education. Do they go out and just support the efforts of NCPIE or is it -- you know, all of the efforts of NCPIE may not make a difference if the advertising doesn't change then, too.

CHAIRMAN CANTILENA: Dr. Wood.

DR. WOOD: Charles, I think the way maybe to handle it would be to say the following, that we talked earlier about the FDA and the company having a joint responsibility to reduce the instance of overdoses from acetaminophen within some defined period, and you ought to come back here, you know,

meaning to the world at large and tell us how you've done.

Now, I think if the company and the FDA come up with an action plan to get that done that includes these things, then the companies involved are likely to be cooperative to do that.

If you come up with some better plan that works just as well, then that's fine, but I think the bottom line here ought not to be this focus on, you know, which things we're going to dicker with rather than recognizing that really the bottom line is reducing the instance of bad outcomes, and that we ought to expect some deliverable to be actually delivered, and that that's the way to get pressure on it.

CHAIRMAN CANTILENA: So, Charlie, if I can just try to pin you down, in terms of this issue of education and the sponsors of the industry responsibility, would it be more helpful for FDA if we voted on the sorts of emphasis that we think should be included in these programs? Is that probably more helpful?

Okay. Then lets craft a question, and I have to admit I'm starting to run on empty. Let's see. I guess the question should be -- please. I'm

on empty.

DR. CUSH: That we recommend that the revisions that have been accepted thus far as they pertain to packaging and display, format and wording should also be equally extended to all advertisements both in print and media. So that would include recognition of the actual name of the product that's included. This product contains acetaminophen. That the cautionary wording that's included, that, you know, if you're an alcoholic or there should be caution about using this with combined products, et cetera, et cetera.

But basically the recommendation we made be extended and included in all print and media advertisements.

CHAIRMAN CANTILENA: Okay. So any discussion on that? Dr. Johnson.

DR. JOHNSON: I would agree with that. I guess the one concern I would have or the one approach I would take with this is that we not focus just on acetaminophen, but that for all of the over-the-counter products, that the risks of those products should be sort of on display just like they are for the Rx products so that it's not just an acetaminophen issue.

Because all of the OTC drugs have certain risk, and so I think it's something that if it can happen, if that can be sort of enforced, it should happen for all OTC drugs.

DR. CUSH: But the problem with that is that those rules, you know, regarding a brief summary as indications and then all of those, you know, common side effects and bizarre side effects, those right now only apply to, by rule, to prescribed products. I don't know if we can extend that without changing legislation and internal rules to -- without major effort -- to these over-the-counter products.

DR. JOHNSON: Right, but I mean, I agree with that, but I also would argue that if that's true, then it can't be changed for just acetaminophen. Those rules won't be changed just for acetaminophen.

So it would sort of either need to be across the OTC class if there was a rule change. It would seem the only logical way to do it.

CHAIRMAN CANTILENA: Okay. Well, in approximately 14 hours, we'll be talking about another class of drugs. Any other comments?

DR. JENKINS: Dr. Cantilena?

CHAIRMAN CANTILENA: I'm sorry.

DR. JENKINS: If I can make a suggestion,

we're kind of bridging into a very unusual area here because this is an Advisory Committee to the FDA, and we've already acknowledged that FDA does not regulate the advertising of these over-the-counter products.

We don't have anyone from the FTC here to articulate their boundaries, their regulations, their rules, and I think it might be better if the committee has ideas about educational efforts or things you might like to see sponsors do in their advertisements, maybe you could articulate those, but I don't really think we need to have a vote on specific recommendations because it's kind of out of context. We don't have the right people here to help us understand the context that we can work in from the FTC.

CHAIRMAN CANTILENA: Right. Yes, thank you for that perspective.

I had asked early on this afternoon if there was a mechanism in place where the information or the recommendations from our group can find their way back to the FTC, and that's why we're going to have this conversation.

But I guess if you would prefer that we just open it up to general suggestions, then I'm fine with that.

DR. JENKINS: But I think at issue here is that even though that's sort of not part of the rules, we're questioning the rules. We're saying that it should fall under the purview of the FDA to oversee how these drugs are marketed and advertised.

MR. GALSON: Let me just say something. Not to disagree with you that that's not the point, but that's the sort of determination that Congress makes, that kind of question, and you're not advisory to Congress.

It's fine to talk about it, but it's not going to do any good really.

(Laughter.)

MR. GALSON: So it --

DR. CUSH: Well, I could start here and then work our way up.

(Laughter.)

MR. GALSON: No. I'm trying to have you all be as focused and effective as possible. The most effective thing you can do is make recommendations to the agency about things that are within our purview.

CHAIRMAN CANTILENA: Okay. Well, we have two choices. We can vote on whether or not to vote or we can just make recommendations or we can go on to the next topic, but I understand your point of view.

Dr. Brass.

DR. BRASS: Yeah. I think this is really straightforward. I think it has been a consistent theme throughout the discussion that there are critical areas that are sources of problems, and that clearly a major component of any risk reduction effort hopefully assessed over time is going to be education, education of consumers, education of health care professionals, broadly based, and I think simply acknowledging that theme without recapitulating all of the specifics I think might be sufficient.

CHAIRMAN CANTILENA: All right. Well, how about at the risk of, you know, wasting our time, if the question were posed such as would all of the recommendations we've made for the reduction in risk in terms of labeling and programs -- are you in favor of having those apply to advertising and consumer education if possible? Is that something that you would vote in favor of?

Is that -- Dr. Wood?

DR. WOOD: Would it be reasonable to suggest that we invite the FDA to explore with the colleagues at the FTC how something like that could be implemented as a recommendation, rather than a recommendation to the FDA?

CHAIRMAN CANTILENA: Yeah.

DR. WOOD: Would that get everybody off the hook?

DR. JENKINS: Yeah, we would be very happy to share with our colleagues at the FTC, who I think Dr. Bull mentioned earlier we do have mechanisms to interact with them, some of the thought that you have.

Again, the reason I think I would like to avoid or make the recommendation that you don't take a vote is we don't have the knowledge they have about the boundaries in which they work. We understand the boundaries under which FDA works. We don't understand the boundaries under which FTC works.

I think it would be best that you help us understand what your concerns are, and we can relay those concerns. I would give as an example even the prescription drugs, when they advertise, they don't disclose every risk associated with the drug. They disclose or are required to disclose the most important risks.

So there's judgment involved. There's a lot of fine detail that goes beyond just making a recommendation that everything you've recommended for the label be included in every advertisement. That may be a very expansive recommendation.

CHAIRMAN CANTILENA: Just a couple more comments, and then we'll actually come to closure on this what I thought was an easy topic.

Dr. Cush.

DR. CUSH: What better way to offer an opinion than to have a vote from the whole committee? And what better way to educate than to sort of direct a marketing effort?

CHAIRMAN CANTILENA: Dr. Alfano.

DR. ALFANO: Let me try to offer a little bit of perspective and actually read something that is a briefing document from CHPA, and it's some comments on the Federal Trade Commission oversight, and I'm actually going to read it because presumably lawyers put this together.

The Federal Trade Commission uses three basic regulatory standards or policies to address consumer advertising:

One, reasonable prior basis, prior substantiation policy under which FTC requires objective claims, express or implied, to be supported by adequate documentation. FTC typically looks to FDA determinations or works with FDA to address OTC advertising issues.

The second two are probably more relevant

to the issue at hand. The first part of this is deception policy, which is based on material representations, omissions, or practices likely to mislead a consumer acting reasonably under the circumstances.

And the third policy is the unfairness policy, which defines unfairness as acts or practices likely to cause substantial injury to consumers and that are not reasonably avoidable by consumers themselves or outweighed by benefits to consumers or businesses.

There's another CHPA piece which really does endeavor to explain why the advertising piece is regulated by the FTC as opposed to the FDA, and the premise is -- you might disagree with it -- but the premise is that they regulate all consumer advertising, and that there's a benefit to the consumer overall that advertising has a consistency to it in terms of the way material is presented, whether you're talking about food or cars or drugs.

And so that's why I believe Congress at some point in its wisdom or not elected to separate those things.

Another perspective is that, you know, the warnings, the true information that the patient is to

use has always been delivered via the label. That's the primary purpose of the label.

Advertising has a different purpose. Advertising is designed to introduce people to new products and to allow for brands to be differentiated in one way or another.

And so probably not too many of you saw this, but if you try to do too much in an ad, you run into the situation that exists now in some of the Rx ads that are on television, which led to one of the funniest "Saturday Night Live" skits I ever saw in which they talked about some fictitious drug, and there was bucolic scenes of the drug making you wonderful and people romping through the woods or whatever, and then they read the side effect profile.

And I remember two of them. The first side effect was seeing the dead and the second side effect was a condition known as hot dog fingers.

And the point is this is society reacting sometimes to overkill on the label, and we could end up -- or the advertising, as the case may be -- with de minimis benefits to the consumers because we've so overloaded them in the desire to try not to leave anything out.

Finally, earlier I pointed to the success

with Reye's. We reduced -- and this was a team effort on the part of the industry, FDA, and the reporters, the reporters in the room. Reye's went down not simply, in my opinion, because of the labeling. There was wonderful consumer advocacy involved at the time.

My recollection is there was nothing in the ads. Okay? It was the Jane Brodys writing in The New York Times. It was the Good Housekeeping articles that, you know, thoughtful parents read so as not to make that mistake in the future.

And that's a model that could be very helpful here. I don't think advertising is the way to effect these changes.

CHAIRMAN CANTILENA: Okay. Thank you.

Just to get really to closure then, I guess what I suggest we do is just say does anyone disagree with the recommendation that FDA consider and/or the sponsors, the industry, work toward applying some of the recommendations and thoughts we've had toward labeling into consumer education and health care, you know, education.

Does anyone object to making that statement? We're avoiding the vote and we're not specifying a pathway. We're just expressing a desire globally.

DR. CUSH: And we're not specifying advertising either.

CHAIRMAN CANTILENA: Right. Well, you know, consumer education.

DR. CUSH: But I think we spent most of today talking about education, and everybody agreed that was what we need to do. So we don't even need a vote on that.

CHAIRMAN CANTILENA: Okay. Well, actually we're not voting. I'm just asking if anyone objects.

Dr. D'Agostino.

DR. D'AGOSTINO: We don't want to lose the educational aspects and so forth and get that carried away or get that mixed in with the advertising because we've been very forceful in the past as a committee in terms of making recommendations for education, and we've been saying that all along.

So really I think this is really sort of the sort of advertising that is at issue, not the education.

CHAIRMAN CANTILENA: So you would prefer that we specify that these recommendations, et cetera, be translated to advertising and consumer education.

Does anyone not agree with that? Should we include advertising and consumer education in our

recommendation?

Okay. Hearing no nays, then I think we shall ask FDA if they've had enough advice for the day.

(Laughter.)

CHAIRMAN CANTILENA: I won't ask the committee if they're ready to adjourn, but I will ask Dr. Jenkins, Dr. Ganley, Dr. Bull. Any other areas that you seek?

DR. JENKINS: I think we've gotten very good advice and information from the committee today. The only area that we didn't specifically go around the room for was the issue of additional studies needed, but I think you've covered much of that in some of your answers to other questions.

So unless people had specific additional suggestions for additional studies they think needed to be done that haven't been addressed already, I think we've gotten the information needed from the committee today.

CHAIRMAN CANTILENA: Okay. Are there any specific areas or types of studies that have not been mentioned that you'd like to suggest?

(No response.)

CHAIRMAN CANTILENA: Okay. Hearing none,

everyone, thank you very much. Thank the sponsors. Thank the FDA staff.

We will reconvene tomorrow at 8:00 a.m.

(Whereupon, at 5:53 p.m., the meeting in the above-entitled matter was adjourned, to reconvene at 8:00 a.m., Friday, September 20, 2002.)