UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

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MEETING

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LABELING AND DOSING OF OVER-THE-COUNTER PEDIATRIC

ANALGESIC/ANTIPYRETIC DRUG PRODUCTS

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THURSDAY, SEPTEMBER 18, 1997

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The Advisory Committee met, pursuant to notice, at 8:30 a.m., in the Ballroom of the Holiday Inn, 2 Montgomery Village Avenue, Gaithersburg, Maryland, Ralph D'Agostino, Ph.D., Chairman, presiding.

PRESENT:

RALPH D'AGOSTINO, Ph.D.	Chairman
THEODORE G. TONG, Pharm.D.	Member
ERIC P. BRASS, M.D., Ph.D.	Member
PATRICIA McGRATH, Ph.D.	Member
LYNN McKINLEY-GRANT, M.D.	Member
MARY ANNE KODA-KIMBLE, Pharm.D.	Member
GEORGE A. BLEWITT, M.D.	Member
MICHAEL WEINTRAUB, M.D.	Member

REPRESENTATIVES FROM THE ARTHRITIS ADVISORY COMMITTEE:

DANIEL J. LOVELL M.D., M.P.H.
FRANK PUCINO, JR., Pharm.D.

PRESENT: (continued)

GUEST SPEAKERS:

CHESTON M. BERLIN, JR., M.D.
TOBY LITOVITZ, M.D.

ON BEHALF OF THE NONPRESCRIPTION DRUG MANUFACTURERS ASSOCIATION:

WILLIAM SOLLER, Ph.D.	Senior Vice President and Director of Science & Technology
SAMUEL M. LESKO, M.D., M.P.H.,	Slone Epidemiology Unit, School of Public Health Boston U. School of Medicine
ANTHONY TEMPLE, M.D.	Executive Director of Medical Affairs, McNeil Consumer Products Co.
RICHARD S. WEISMAN, Pharm.D.,	Research Associate Professor of Pediatrics, University of Miami School of Medicine
RALPH KAUFFMAN, M.D.	
WAYNE R. SNODGRASS, M.D., Ph.D.	

PRESENTERS FOR THE FDA:

DEBBIE LUMPKINS	Division of Over-the-Counter Drug Products
E. DENNIS BASHAW, Pharm.D.	Division of Pharmaceutical Evaluation III
ROGER A. GOETSCH, Pharm.D.	Division of Pharmacovigilance and Epidemiology

I-N-D-E-X

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

(8:30 a.m.)

CHAIRMAN D'AGOSTINO: Good morning. I'm Ralph D'Agostino, the Chairman of the Nonprescription Drugs Advisory Committee. Is this mike giving an echo?

This meeting is a meeting of the Nonprescription Drugs Advisory Committee, with representation from the Arthritis Advisory Committee, and we're going to be considering labeling and dosing of over-the-counter pediatric analgesic/antipyretic drug products.

What I'd like to do now is ask the people around the table, the FDA and the panel members and the guests, if they would introduce themselves, speaking into the mike so that the transcriber can get your position and also see if the mike is working correctly. Dr. Katz, would you please start?

DR. KATZ: I'm Linda Katz, Deputy Director of OTC Drugs at the FDA.

DR. WEINTRAUB: Mike Weintraub, Director of the Office of Drug Evaluation Number V.

DR. McKINLEY-GRANT: I'm Lynn McKinley-Grant. I'm a dermatologist in Washington at the G.W. and Washington Hospital Center, and I'm a member of

the Nonprescription Drugs Advisory Committee.

DR. PUCINO: Frank Pucino from the Pharmacy Department at the National Institutes of Health, and I'm with the Arthritis Advisory Committee.

DR. TONG: Good morning. I'm Ted Tong. I'm a member of the Nonprescription Drugs Advisory Committee, and I'm from the University of Arizona, College of Pharmacy and Medicine.

DR. NEAL: Good morning. Andrea Neal. I'm the Executive Secretary to the Committee.

DR. SILVERMAN: I'm Earl Silverman, a pediatric rheumatologist from the Hospital for Sick Children, University of Toronto.

DR. McGRATH: Hi. Patricia McGrath from the University of Western Ontario, a member of the Non-Drugs Prescription Advisory Committee.

DR. KODA-KIMBLE: Mary Anne Koda-Kimble from the University of California at San Francisco, School of Pharmacy, and I'm a member of the Nonprescription Drugs Advisory Committee.

DR. BRASS: Eric Brass, Harbor UCLA Medical Center, Nonprescription Drugs.

DR. LOVELL: Dan Lovell, pediatric rheumatologist, University of Cincinnati, member of the Arthritis Advisory Committee.

DR. BLEWITT: George Blewitt, industry representative to the Nonprescription Drugs Advisory Committee.

DR. LITOVITZ: Toby Litovitz, Executive Director of the American Association of Poison Control Centers.

CHAIRMAN D'AGOSTINO: Thank you. Now we'll have the meeting statement read by Dr. Andrea Neal.

DR. NEAL: Good morning. Before I read the statement, I'd just like to repeat that the meeting that had been scheduled for tomorrow with the Pulmonary, Allergy Drugs Advisory Committee was canceled.

I would also like to announce that our consumer representative, Kathleen Hamilton, had a death in the family, and as such, is not here today.

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

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and

Research present no potential for a conflict of interest at this meeting, with the following exceptions.

In accordance with 18 U.S. Code 208(b)(3), full waivers have been granted to Mary Anne Koda-Kimble, Pharm.D., and Ralph D'Agostino, Ph.D. A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

With respect to FDA's invited guests, there are reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Toby Litovitz would like to disclose that, as the Executive Director of the American Association of Poison Control Centers, she is involved in TESS status searches and sales to nearly all the firms which manufacture over-the-counter analgesic and antipyretic drug products.

Dr. Litovitz is also the principal investigator for a funded post-marketing surveillance project for Nicotrol, a product of McNeil Consumer Products Company. Further, in 1997 Dr. Litovitz served on a pediatric analgesic/antipyretic

consultants board for McNeil Consumer Products Company. She attended a one-day meeting for which she received an honorarium.

Cheston Berlin, Jr., M.D., would like to disclose that he consulted one time for Ascent Pharmaceuticals, and he is a member of Pfizer's Speakers Bureau. Further, he is a member of the Pharmacy and Therapeutics Committee for Rite-Aid Corporation.

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

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

Thanks.

CHAIRMAN D'AGOSTINO: Thank you. Now we'll have opening comments by Dr. Michael Weintraub.

DR. WEINTRAUB: Thank you, Ralph.

I just wanted to say how much the FDA appreciates your coming for one day, and we know that

the cancellation of tomorrow's meeting did raise some -- make your lives a little more complicated, but we appreciate your coming here for the one day, and thank you very much. Good morning.

CHAIRMAN D'AGOSTINO: You're not going to give us insight into the -- Then why don't we move right to the FDA presentations, and get all the insight from them.

We have three speakers. Hopefully, everyone has the agenda in front of them. We'll start off with Debbie Lumpkins.

MS. LUMPKINS: Good morning. I've been asked to give you some background information on the agency's regulation of OTC pediatric analgesic/antipyretic drug products.

Prior to the initiation of the OTC drug review on May 11, 1972, the agency made a number of interpretive statements concerning warnings and cautionary information for drugs and devices offered for OTC sale.

Included among these statements were the above cautionary information that recommended three years of age as the minimum age for administration of OTC salicylate containing products without a physician's guidance. Manufacturers were given the

option of using one or the other of these recommended statements.

For OTC products containing acetaminophen, the agency required the following warning against the use of acetaminophen in children under three years of age. Both required -- Both the recommended cautionary statement and required warning are currently included in Title 21, Section 369 of the Code of Federal Regulations.

As part of the agency's OTC drug review, the advisory review panel for OTC, Analgesic and Antirheumatic Drug Products or the Internal Analgesic Panel developed pediatric dosing schedules for products containing acetaminophen, aspirin, carb aspirin calcium, choline salicylate, magnesium salicylate, and sodium salicylate.

The pediatric dosing schedules recommended by the panel shared the following common characteristics. Dosing was based on age. The minimum age for dosing was two years of age. The adult dosing started at 12 years and above. Dosing was to be done every four hours, and there was a maximum of five doses daily.

The age range of the pediatric dosing reflected the panel's adoption of the recommendations

of the Advisory Review Panel on OTC, Cough, Cold, Allergy, Bronchodilator and Antiasthmatic Drug Products.

The panel recommended OTC pediatric dosing down to two years of age, and that adults be defined as 12 years of age and older. The panel's recommended pediatric dosing schedules were adopted by the agency and included in its proposed rule for OTC internal analgesic and antipyretic drug products published in the Federal Register of November 16, 1988.

Prior to the publication of the proposed rule, the agency published a Notice of Intent on June 20, 1988. In that Notice, the agency indicated that it was considering proposing a rule concerning dosing information in the labeling of OTC drug products for children over 12 years of age, and solicited the submission of comments and information relating to this issue.

In response to the agency's Notice of Intent, a number of suggestions were received that included several different approaches to the across-the-board pediatric labeling.

On January 13, 1995, the agency sought the advice and recommendations of its Nonprescription Drugs Advisory Panel on several issues relating to

pediatric labeling. Among the issues that the agency sought the committee's advice on were: What is the preferred basis for determining OTC systemic pediatric dosage and labeling; examples, age, weight, height or length, body surface area or combination of these? What is the minimum age or weight that should appear on OTC product labeling, and should this minimum age be different for certain classes of drugs, such as internal analgesics or antihistamine?

The committee provided the following advice. Weight should be the preferred basis for dosing, if it is known, but age ranges should also be given for those where weight is not known. Minimum age should be determined on a case by case basis.

Currently available on the OTC market are a large number of analgesic/antipyretic drug products in an array of dosage forms that include chewables, suspensions, drops, and suppositories. Today's meeting will focus on the pediatric use of some of these products, specifically addressing infant drops that are approximately twice as concentrated as children's suspension.

The labeling samples provided to you this morning will illustrate the critical issues at hand for today's discussion. These are:

Given the safety implications discussed for OTC analgesic/antipyretic suspension and double concentrated drops, should labeling for overlapping ages be permitted?

What labeling information, modifications, do you suggest to prevent unintentional overdose?

Can single ingredient analgesic/antipyretic suspension products be safely and effectively labeled for use in children less than two years of age; and if so, what is an appropriate lower age limit?

Also, are there any other labeling recommendations that you have?

That brings us up to what we need to do today. Thank you very much.

CHAIRMAN D'AGOSTINO: Thank you, Debbie. Now we're going to hear from Dr. Dennis Bashaw.

DR. BASHAW: Good morning. I'd like to thank the Committee for inviting me to speak today. I've been asked to speak on the overview of the pharmacokinetics of OTC analgesic/antipyretics, primarily focusing on ibuprofen, acetaminophen and, to some extent, for historical basis, aspirin.

You've been provided in your package a two-page overview which I gave to you, and also a

couple of articles which I tho ught were the best from the published literature.

What we're faced with is mostl y drugs not really having a good database of published informatio n in terms of the pharmacokinetics. Given the hour of the morning, I won't go into any models or derivation s of that. I promise you that. So the next overhead, please.

Just, you know, to follow on Debbie' s background, you know, the age we're focusing on here today, just for a quick overview -- I'm sure we're al l very familiar with them, if not from persona l experience, from our practices.

Aspirin, of course, is the oldest agent i n this class, being developed and used in Europ e sometime around the late 1890s, early 1900s. O f course, in this country its use in the pediatri c population has certainly declined from what it onc e was, due to the association with Reyes Syndrome.

Acetaminophen is today the primary OT C analgesic/antipyretic used in the pediatri c popula tion. One of the complicating factors was , whenever you talk about any of these products, bu t especially with acetaminophen or even ibuprofen is th e multitude of dosage forms that are available.

Just looking through the nonprescription PDR the other day, I think there was like three pages of acetaminophen dosage forms and products that were available. A lot of times you look at different manufacturers and you look at delivery systems, suspensions, suppositories, etcetera, whenever we talk about the pharmacokinetics. It's both the kinetics that are inherent in drug itself and delivery system.

Even though the OTC marketplace is primarily immediate reliefs, there is variability between the dosage forms, and that's always a complicating factor whenever we're talking about these issues.

Also, finally, ibuprofen is probably the drug -- You know, it's clear from marketing the OTC in the 1990s -- is the one we have primarily the best database, primarily because aspirin and acetaminophen, because of their time of development, obviously, preceded the FDA, preceded New Drug Applications, but ibuprofen was developed at the time originally for prescription marketing where we do have prescription database, where there were publications, and there is published data that we can refer to, to some extent.

Next, please.

When we start talking about these issues,

one of the issues I was asked to address was age-related pediatrics and pharmacokinetic changes in these groups. How well can we extrapolate from the adult data to children? Is that possible? What is even extrapolation among pediatrics, among the age range we're talking about here?

You know, there's some use in the very young, less than a year, and the OTC labeling has certain indications also for what is considered OTC use, looking at what can we say from the data from it.

Next, please.

This is not intended to be read here, just to give an overview. This is a table from the pharmacokinetic basis of drug treatment, which really summarizes some of the physiologic changes that happen during maturation.

You can see there, we have changes, of course, in absorption, distribution, metabolism, elimination, that really vary throughout the maturation process. You can see the differences from premature, newborn, one-year-old. A number of physiologic changes happen in this population, such that there's always a question of how well can you extrapolate, how low can you go.

It really -- This overhead is just t

intended to bring, of course -- remind the committee and bring to the attention of the group the wide variety of things and factors that can happen and always must be considered.

We primarily have been focusing, looking at altered metabolism, not so much for the absorption because most of these things are formulated fairly well, so they are immediate reliefs and do relief s very quickly; but we are very concerned with metabolism, and especially with acetaminophen because of its known hepatic toxicity, the metabolic route of it and how it goes and to what degree -- There has always been speculation as to safety valve in the very young child of sulfation, how well that really works. Is it really quantifiable, and to what extent?

Next overhead, please.

Now that's just a summary. When we're talking about metabolism, we usually get focused on what we call cytochrome P-450 and P-450 metabolism. This overhead is just to give perspective, but there is certainly many, many different mechanisms of drug metabolism, and we really, to some degree, know some information about maturation in some of these enzyme systems; others, we don't.

Some children are born with fully intact

systems. Some take a couple of years to mature. Some don't mature or go under changes in puberty. So metabolic status is a concern we have, and it's not just limited to cytochrome P-450 but really covers the whole gamut of possible metabolism routes.

Next overhead, please.

The problems we have, when one goes back to look at the data, is again the fact that there's really -- you look at it from drug related and population related issues, that again these are old products. They were developed prior to pharmacokinetics as a science, which was really probably, depending on which author you want to quote, sometime in the mid-seventies, '75 or '77.

There is data for some of the newer products like ibuprofen in NDAs, but a lot of that data has never been published. It's been kept in the files. So its availability out there to the prescriber and to the public and to those who need to know has been somewhat restricted.

Also, there's always a question of doing these studies in these populations. Doing studies in children always raises a whole number of ethical issues, you know, disease state, informed consent, blood volumes, a whole gamut of issues that are always

raised when one starts trying to do pharmacokinetic studies in the pediatric population.

One thing, I think, that we do have an ability, and I think we'll focus on today, is when we're talking analgesic/antipyretics, the information I'll be showing today is primarily related to the antipyretic use of these agents, which again, from a pharmacokinetic standpoint, probably represents the more severe cases; because as one is, certainly, aware of, there are temperature/fever related changes in drug metabolism such that the use of these drugs in the child with fever probably represents a stressed system, which is probably more relevant to look at.

We're going to be presenting some data here, both from the published literature and also some mean data from NDAs. We really could not -- because of the nature of it and the open public forum, could not provide the raw data, individual subject data; but we will provide some NDA data in a mean format to provide some background to give some context to it.

To anticipate one of the group's questions, because once you see the database there will be questions of why there weren't some correlations made, why there weren't some additional analysis done -- To anticipate that question, the

primary reason was that the st udies we're going to be talking about were not intende d to look at the effect of age.

They were done for formulatio n development. They were done with different sampling techniques and different sampling objectives, suc h that, although we were able to calculate simpl e pharmacokinetic parameters, area, clearance, etcetera , trying to make detailed analysis and do trend analysi s -- you know, trying to rank th em from two years to 30 or two years to 18, those kinds of comparisons , because they're form different studies that were neve r inten ded to be combined -- they have differen t sampling objectives, and different techniques wer e employed -- it made the combination a little bi t inappropriate.

So you may look at this and sa y, gee, you could have done more. In a way, yes, but in a way, w e also felt it would be misleading. So we're just goin g to present the data as we have it, and try to take yo u through it.

The next overhead, please.

The suspension really doesn't belong o n here. Some of the data does come from suspension, bu t it should be ibuprofen liquid dosage forms. I didn't

catch that until this morning.

What we have here is a table of some comparative pharmacokinetic parameters. The Brown article is one of the two articles that was provided to you in your package, which provided some of the best published pharmacokinetic information on ibuprofen.

As you can see, he had groups of 44 and 49 subjects ranging from three months to 12 years, at both 5 and 10mg per kilogram rates, and we have for Cmax, Tmax, clearance, and half-life values.

There's a smaller article from Nahata which I did not provide to you, because of the small size. I didn't want to overburden it. We also have data from two different NDAs, looking at the pharmacokinetics in children and also one study in adults.

You can see, there is some comparison in terms of you look at, you know, time of absorption, you look at what peak levels you get. There is some similarity, but also some significant differences.

It's interesting to note that on a 5mg per kilogram basis there's certainly increased levels in adults. Now whether or not that's due to the clearance or suspected volume change is really y

unknown.

If we could have the next overhead, I think we'll see it a little bit more graphically.

The solid lines here represent NDA data which -- these are the mean curves from those studies. The individual block points there are data from the articles which we did not have to access to the raw data. We had to interpolate them. So I tried to put them as points so they're not quite so heavily weighted.

You can see there that, looking at the comparison for 5 mg per kilogram, certainly, in the pediatric data, which is the blue line and the orange blocks, there is some similarity, and there's also quite a bit of difference; but there's also quite a large population associated with the blue line, and a much smaller population -- I think nine subjects -- with the orange.

So there's some similarity but some difference there. Clearly, when you get to adults and you look at what their dosing was, they only got 3mg per kilogram, but they were very similar to pediatrics.

In fact, if you were to do some simulation work, which I didn't want to put on here because it's

a little bit more detailed than I wanted to get into this morning, adults would have significantly higher levels on a 5mg per kilogram b asis, again pointing to there being some kind of age-related change wit h ibuprofen.

Whether or not -- Where exactly thi s occurs -- Is it a gradual change or something tha t occurs at puberty or what? -- is really unclear right now. Again, the data was not -- This data was no t collec ted for that type of analysis. So we didn' t pursue it very far.

Basically, it shows that for ibuprofe n there is some difference, although exactly what th e nature of it is, we're not qui te sure. There is some difference between adults and children in thei r pharmacokinetics.

It doesn't appear to be a clearanc e mechanism. I really, personally believe -- I could g o into it, but I don't want to right now -- that it' s probably more related to volume changes.

Next overhead.

Turning now to acetaminophen, again using the Brown data we see we have data from four differen t -- two different studies and two NDAs here, where we have pediatric data from three years -- three months

to 12 years, two years to seven years, two years to 11 years, and then some comparative data from adults from 18 to 50.

All these doses, with the exception of Wilson are approximately 12mg per kilogram. One that's rather interesting here is the fact that we have good agreement again in peak levels and systemics, also in half-life.

I think this is more visible again, if we look at the next overhead with the graphics. It's very clear that, when you look at, again, the mean adult data -- I'm sorry, the line above is sort of bluish, but the top line is actually cyan, and the next line is dark blue.

There's a comparison of the adult and pediatric data. There is quite a bit of correlation there for very similar doses, suggesting that between children and adults with acetaminophen that degree of exposure is directly related to body weight, and that a 5mg per kilogram dose or whichever, 10mg, 12mg, would give apportional levels between children and adults.

Again, no differences were seen in clearance, and even the other data, if you were to take the -- I know it's hard to distinguish, and I

don't have a pointer here, but if you'll bear with me while I walk away from the mike for a second -- If one was to take the 10mg per kilogram data here and one was to scale it up to approximate the dose, it would start to approach the other lines --

CHAIRMAN D'AGOSTINO: Would you just repeat that so that the transcriber can --

DR. BASHAW: What I was indicating to the committee was that there is data on this graph which represents a lower dose, 10mg per kilogram, from some of the published articles. If one was to scale that information, the mean data would certainly come up and not quite reach the same levels that were seen with the other two treatments, but would certainly be very close to it, not bioequivalent, by any standpoint, but certainly would be within the range.

Considering that we have quite a bit of variability all around these mean lines, there really seems to be quite a bit of agreement between the pediatric and adult data from acetaminophen.

Next, please.

Quite frankly, for aspirin there is not any comparable data. In looking through the literature, the best article that I could really find -- it was on a bias again with the ones provided to

you in your package, which really was not a detailed treatment of aspirin pharmacokinetics in children, but in fact looking at the literature there really is not, and going though the NDA database, again because of the age of aspirin, the fact that there hasn't been a lot of new aspirin NDA products that have come out recently -- in fact, there's not been any -- there is not good data we have on the aspirin pharmacokinetics in these populations.

Clearly, we do have adult aspirin data. I mean, there are pharmacokinetic data, but in terms of being able to make some comparative relationships, as we have with ibuprofen and have suggested with acetaminophen, that really is not possible from the database that we have access to.

Next overhead, please.

Finally, I guess it's -- You know, trying to summarize what we do know about aspirin and the other analgesics is that, aspirin again, there's minimal pharmacokinetic data in adults, and we have no useful pharmacokinetic data in pediatric populations.

When I mean useful, there I'm talking about large studies with good calculation of parameters. There are certainly a few articles here and there and a couple of case reports, but one is

looking for a study on the order of what the Brown study was with 44 patients or even the Nahata study which had a total of 17 patients. There really is not that kind of published information out there that's readily available.

In terms of acetaminophen, there is published data and pharmacokinetics that we've provided to you. There is some evidence, both from the OTC and NDA database that suggests that there are stable pharmacokinetics across the age, and that it is really the body weight.

The metabolic differences in infants: You know, in trying to look back at that issue about what degree sulfation really plays a role, there really is not any hard numbers on that. A lot of that comes from a 1984 article by Dr. Rumack looking at the outcome from overdosing where there was a suggestion, and he speculated that it seemed that younger children, you know, fared better.

The assumption -- Later investigators followed up and suggested that sulfation provided a so called safety valve in the case of overdose, that the children were able to metabolize it through a sulfation mechanism that adults somehow lost at puberty, most likely.

It probably is that, to some degree. How quantifiable is it is really unknown. It's not, I think, a very extensive safety valve, if one wants to call it that. It does exist, but it's really never been quantified, and it would be very difficult to quantify it.

Ibuprofen: There is a considerable amount of published data, and there is comparative data from the NDA database that suggests age related changes in volume. Like I say, a lot of how this information was gained was not so much in the sponsors and the NDA people working on the immediate release dosage forms, but as they were working on different potential controlled release formulations, they used the immediate release's reference products. That's how we gathered most of this information.

Because of the fact that the material is proprietary information, we've had to be a little bit careful of how we expressed it today in presenting just mean data and just mean curves. Honestly, there is more data that stands behind it, but because of the nature and this being an open public meeting, I really was not able to get into the exact database and what the results really looked like on a variability basis.

That concludes my presentation.

CHAIRMAN D'AGOSTINO: Thank you. Any questions? Then why don't we move on to the third speaker. Roger.

DR. GOETSCH: Good morning. My name is Roger Goetsch. I'm with the Division of Pharmacovigilance and Epidemiology. We'll get our slides going here.

Okay. Today I'd like to -- I've got like half an hour, which is great, to talk to you about post-marketing safety of the three products we've talked about. Usually, what I'm going to use is FDA's spontaneous reporting system data that we collected back from 1969 up to the cutoff date of August 5th of '97.

Just to give you an idea of what I'm going to talk about today is to let you know what the limitations of the SRS is, a little bit of the caveats that would go with the presentation. Then I will talk about children, acetaminophen overdoses, ibuprofen overdoses, aspirin overdoses, and then try to sum it up with a brief conclusion of what we can make with this observational data and kind of what we can't make any conclusions.

The limitations of the spontaneous reporting system is the fact it is a spontaneous

reporting system. It was started in 1969 and has presently gone on with multiple changes in the database.

There's a vast under-reporting, as we'll talk about a little bit later, and we'll also see that reporting is usually decreased with marketing age. This is very important as we're talking about drugs that have been out there for many years.

Reporting usually -- The limitations of the causality is sometimes very hard to determine. Variability, incomplete reporting is also a factor that we have to address. The spontaneous reporting system's main function, and how we use it in FDA, is a signaling, mainly for new chemical entities. So we're kind of using this in a little different light.

One of the things I do want to talk about a little bit is marketing age, when we're talking about decreasing over marketing time. You have to realize with acetaminophen, in 1952 that was when it was the first prescription elixir.

There's probably 200 products now out on the market that has acetaminophen. What we'll find out in the spontaneous reporting system: Most of our reports were seen in 1977. Ibuprofen was a prescription in 1972. In '84 it was okayed by the FDA

for an OTC in the adult population, and in '89 the prescription for children was approved, and just recently in 1995 the OTC children product was approved.

We saw most of our adverse events with ibuprofen in the last two years, '96 and '97. Aspirin, as Dennis alluded, has been out there for many, many years, and it's going to be very hard to make any correlation with aspirin.

The caveats: What we looked at, looking at the spontaneous reporting system: We only addressed single ingredients, and we addressed anytime that that single ingredient was seen as a suspect drug, whether it was an over-the-counter preparation or whether it was Rx preparation.

We kind of divided it up into three children's groups, 0-2, 3-6, 7-12, because we realize that children are not all the same.

A couple of factors that we really have to look at with looking at this data is in 1972 one of the main things that stopped overdose, medication errors, was the child resistant packaging. Also, as Dennis alluded, with aspirin Reye's Syndrome, pretty much acetaminophen replaced aspirin in the children's use.

Also to bring to your attention on acetaminophen, one of the sponsors had received a waiver in 1987 that all they had to do was report fatal overdoses, and that's important to look at when you're looking at the numbers.

The FDA or the agency started looking at medication errors within the SRS in 1993, and we collected data from that. So we're going to try and combine both medication errors and overdoses to give you a good picture.

The last and probably the most important thing: Even though I'm going to be talking about these three products, you really cannot compare them. You cannot compare them in safety. We're just using these as example, and try not to make some comparisons.

The definition of overdose we're going to use today is the accidental overdose where they self-ingested more of that product or the medication error where the dosing error was caused by a therapeutic usage but was given more than was recommended.

Acetaminophen in children made up about nine percent of the total reports that we have in the SRS for acetaminophen. Where it says two years, that should be -- Anytime you see the two years will be

equal or less than two years.

So from this, you can see that we've had probably 23 percent fatalities in children with 11 3 reports in the less than two, and of those 30 of them were fatal. You can see in 3-6, 118, 16 and 66. We saw, as they got older -- in the 7-12 year-old, we sa w that those were almost suicidal attempts. So that wa s a little bit different.

Acetaminophen overdoses: We had 94 o f them, which made up 32 percent of the total children acetaminophen reports. These are the top ten adverse events we used to put them int o the database. We had 37 percent fatality.

As you can see, the prominent event that you'll see is pretty much the liver toxicity, th e hepatotoxicity that we've mentioned earlier.

We looked at serious overdoses, which wer e 53 reports, and broke them down into whether they wer e medication errors, accidental errors, or we couldn't make any determination. As you can see, with the les s than two years old and the 3-6, most of those wer e medication errors. As I said before, that's usually where they were taking it for a therapeutic use, but for some reason or other, they were overdosed or give n too much.

We looked at specific or selec ted reports that had complete data regarding dose, weight an d duration. These are some examples. This will sho w you what we're dealing with. It's a very smal l selected group, and you have to realize, this i s observational data only.

You can see, the HF is hepatic failure . The D is death. The ARF is ac ute renal failure. The most outstanding part is the formulation, that these small children, seven months old, there years and up to six-year-old, are given adult dosage forms.

This is probably -- If I bring any point home, this is the kind of point that I want to mak e sure that everybody understands. All of these had a dose greater than 150mg per kilogram body weight.

You can see the duration range was betwee n one day and seven months. So this is something that happens fairly rapid, and is of a great safet y concern.

Just to give you an example -- and this i s not to scare you or anything e lse, but this is one of our better examples of a 14-month-old that wa s admitted with signs and symptoms of hepati c insufficiency after ingesting the suspension drops of acetaminophen, just for over a period of 48 hours for

a viral infection.

Unfortunately, her liver disease was so bad that she had to have a transplant and, luckily, this young person recovered, just to give you kind of an impact of what we're looking at.

Now switching over to ibuprofen, we looked at the children's reports, which was 1218, which made up about 10 percent of all the ibuprofen reports that we have in the database. Again, the two-year-old is less than equal to two.

We had a lot more reports, 522 reports, but we only had 11 deaths, which gives you a one percent fatality within the children's group.

Looking again at the overdoses of ibuprofen, there's 219 reports. This made up 18 percent of the total children reports that we had in the SRS, a one percent fatality. Next to actually being an accidental overdose, the most prominent adverse event was metabolic acidosis, was your renal involvement.

We also looked at the serious overdose reports, which we had 26, which was 12 percent of all the children overdoses. You can see, it was a little bit different. It was very few medication errors, and most of them were accidental, self-administered

ingestions, and we had 21 reports in the less than two-year-old.

To give you an example again of what we're talking about, we had a seven- month-old male that had a persistent cough for three days, went to the physician. He recommended the three to four teaspoonsful of children's Motrin to be given every six hours for four days.

The doctor, thinking he was going to give 44mg per kilogram per day, the patient went out and bought the oral drops which produced twice the concentration that was intended. The patient experienced what you would expect. They called the physician. He then lowered the dose, and we had a good outcome of this, but this is kind of the example that we want to bring across where you have two products out there that have tow different concentrations.

Now we'll talk about aspirin, just very adverse events for it. We had 75 children adverse events, which made up 3 percent of all reports that we have in the database. We had one percent fatality, less than two-year-old. We had 22 reports, but we had very few reports to make any kind of comparison or any kind of determination on aspirin.

Aspirin overdoses: We only have five in the system, and they were accidental overdoses where they self-administered, ingested too much. This accounted for about six percent of the childrens reports.

To give you an idea just what happens with aspirin toxicity, we had an 11-year-old female that was administered aspirin, adult dose, 325 every six hours for rheumatic heart disease, and she was hospitalized with overdose. They treated, and she recovered. We really don't have a lot of data on aspirin.

So conclusions: What does this all mean? What can we do? The only thing that we can tell from this observational data is that acetaminophen is related, associated with hepatotoxicity when given two to three times the normal dose.

We're seeing it mainly when it's used in a therapeutic treatment, actually, for fever or viral infection, and we're finding that there's a problem with formulation, that these small children are receiving adult formulation or are receiving a formulation that wasn't intended.

Ibuprofen: We see that it has a nephrotoxicity, a metabolic acidosis, and most of the

accidental ingestions are from the suspension given instead of the drops. We find out that these patients recover very well, where the acetaminophens have more problem.

Aspirin: With Reye's Syndrome, pretty much replaced by Tylenol, and all we saw was accidental ingestion.

Thank you very much.

CHAIRMAN D'AGOSTINO: Thank you. Are there questions? I want to thank the FDA for the fine background material and the presentations. Are there any questions?

DR. BERLIN: Yes, I have a question, please. Berlin, Hershey.

Seventeen children died from ibuprofen, but you didn't mention what they died from.

DR. GOETSCH: Oh. They died from hepatic failure.

CHAIRMAN D'AGOSTINO: Could you speak into the mike?

DR. BERLIN: Hepatic failure?

DR. GEOTSCH: Yes.

DR. BERLIN: In ibuprofen?

DR. GOETSCH: No, metabolic acidosis. Excuse me.

DR. BERLIN: Could you be a bit more precise about how they died?

DR. GOETSCH: Yes. It was definitely acute renal failure brought on by metabolic acidosis.

DR. BERLIN: Thank you.

CHAIRMAN D'AGOSTINO: Any other comments? Yes?

DR. KODA-KIMBLE: I wonder if you could address the observation that in ibuprofen most of the deaths or serious events were related to accidental over-ingestion versus medication errors in the acetaminophen group. I mean it seems to me that both have pediatric doses, and both have adult doses. Is it just because ibuprofen seems to be less toxic, and you have fewer reports?

DR. GOETSCH: I think both of those are an issue. I think the less toxic, we've seen that, because most of the cases we saw recovered after they were rehydrated, and the nephrotoxicity was reversed.

We also saw that what was happening, too, was the formulation. You have to realize that the Rx OTC for children has only been out for a couple of years. So a lot of them were ingestion of -- accidental, where they took an open bottle of adult ibuprofen.

DR. KODA-KIMBLE: So you believe that it was pretty clear to parents that ibuprofen was not indicated for kids, because parents are giving adult acetaminophen to kids?

DR. GOETSCH: I didn't really -- I couldn't make that correlation.

CHAIRMAN D'AGOSTINO: Can you hear that all right?

DR. GOETSCH: I really couldn't make that correlation. We saw it more in acetaminophen where the mother would start with the drops, and they would run out of the drops, and they would go ahead and give adult tablets. Now with the ibuprofen, we really didn't see that.

The most stunning thing we did see was with the drops and the suspension interchanged or where they would give a chewable tablet and use an adult strength.

DR. WALSON: Phil Walson from the Ohio State University.

Did you look at all for two things: Coingestants, including other antipyretics, and did you evaluate -- I'm sorry. Did you look at all for coingestants, including other antipyretics or herbal products, etcetera; and did you evaluate, when there

were data available, such as blood levels, the correlation between history and objective measures of dose?

DR. GOETSCH: Okay. We only looked at variance, and we didn't look at any herbal or anything to make it more of a clean data. We did get some reports that had blood levels --

CHAIRMAN D'AGOSTINO: I don't think we'll take anymore questions from the floor.

DR. GOETSCH: We did look at cases that had blood levels, but as you know, with acetaminophen blood levels in the first 24 hours, 48 hours, really doesn't tell you a whole lot. You would have to go out to the 72 hour, looking at toxicity.

For ADRs and adverse events, a lot of our case reports came in from the consumer, came in from the health professional, and basically had very limited data. The only ones that we had clear data were the fatalities.

CHAIRMAN D'AGOSTINO: Are there other questions from the panel? Maybe when the industry makes its presentation, if there's some questions that they would like to bring up, it would be useful at that time, but I'd rather keep the discussion to the table right now. Are there other comments?

Then let's move on to the next speaker . Dr. Toby Litovitz will make a presentation. Now she has passed out material which, I believe, is in front of us all. Is that correct?

DR. LITOVITZ: Could we have the lights on? Thank you.

I'd like to begin by giving you some background on the test database. Many of you are unfamiliar with it.

The database was piloted in 1983, and then implemented in 1984. I'd like to first turn to this annual report for 1996 of the test database, and to look at Table 1 on page 448. You'll see that there's been a rather dramatic growth in the size of this database from about a quarter- million reports in 1983 to 2.1 million in 1996.

There are 75 poison centers currently operational in the United States. Sixty-seven of them participated in the test databases in 1996, covering 87 percent of the U.S. population.

There are -- Of the 75 U.S. poison centers, 48 are certified poison centers, meaning they meet minimal national standards. They have 24 hour dedicated staff, and by dedicated I'm not referring to behavior, but rather to the fact that they are doing

poison center operations rather than filling scrips in a pharmacy and answering a phone in between or seeing emergency department patients.

They are staffed by specialist in poison information who become certified by sitting for a national examination after a year's experience. They have back-up by a board certified medical toxicologist, and they do follow-up on cases.

They don't just receive an initial phone call and give a recommendation. They actually call back to make sure that the patient did as expected and that the recommendations were followed and provide additional information, both to calls from the home and from health care facilities.

There is comprehensive charting in these facilities and data submission to the test data base, with a medical record maintained in the poison control center.

About half of the test participants used this data collection form that you have in front of you, which is a paper form. It has one side the data section that can be bubbled with a high carbon marker, detached, and run through an optical scanner. The other half of the test participants rely on a computerized data collection system and submit their

data electronically, directly electronically.

Turning in the same report to Table 2 on page 449, you can see the site of color, which in the vast majority of exposures in this database is the patient's own residence, and -- I'm sorry. That site of exposure is most always the patient's own residence, and you can see about 13 percent of cases are actually called in from health care facilities.

Turning to Table 3, the age distribution of the database overall shows that 53 percent of cases occur in children under the age of six, but these children are responsible only for four percent of the fatalities in this database, and about 61 percent of poisoning fatalities occurred in 20-49 year-olds, giving you the obvious idea that these are predominantly intentional.

Turn to Table 5 on the next page. You'll see that multiple substances are implicated in about 7.2 percent of cases. This database only collects specific product information on the first two substances implemented -- or implicated.

So we have the opportunity to analyze test data both with concomitants and without concomitants, depending on whether we're looking to see the broad universe of exposures or to home in on the specific

toxic manifestations of a particular compound.

Table 6 shows that 85-86 percent of cases are unintentional, but most adult deaths, 79 percent of adult deaths, are intentional. You can see the distribution of reasons for the exposure, and 123,000 cases in this database are therapeutic errors, which is what we'll focus in on today.

the test definition of a therapeutic error is slightly different from the definition the FDA is using. We consider a therapeutic error an unintentional deviation from a proper therapeutic regimen that results in either the wrong dose, in incorrect route of administration, administration to the wrong person, or administration of the wrong substance.

Drug interactions resulting from unintentional administration of drugs or foods which are known to interact are also included in this database as therapeutic errors. There were an additional 32,000 adverse reactions to drugs reported here.

Table 9 from the annual report shows the route of exposure. Multiple routes can be coded for a given case, and most exposures are ingestions.

Table 10 shows the management site. Most

cases are managed at home or at the site of the exposure, about 74 percent of these cases. The highest level of care rendered to a patient is coded here.

So, for example, a patient seen in a health care facility goes in through the emergency department, admitted to the ICU, then transferred to a medical floor, and then to the site facility, is coded as receiving critical care. That's the highest level of care.

Medical outcome is shown in Table 11. It is the variations in the distribution of medical outcome from product to product that are really key to our efforts to identify hazards. We have two different kinds of medical outcomes. There are definitive outcomes such as no effect, minor effect, moderate effect, major effect, and death.

Then there are nondefinitive outcomes where the patient was not followed, either because the exposure was so nontoxic that the specialist handling the call felt that no follow-up was required or because minimal toxic manifestations were expected.

There are also a smaller number of cases that are not followed that are potentially toxic, and these routinely are patients who refused follow-up,

refused to give a phone number, so follow-up wasn't possible, and a small number of cases coded as unrelated outcomes as well where the symptoms were deemed related to something preexisting or some other cause.

Now so that you can follow the rest of this discussion, we need to define the terms minor, moderate and major effects. The minor effects are minimally bothersome. They generally resolve rapidly. They leave no residual, and require minimal treatment.

At the other extreme, we have the major effects. These are life threatening or have residual disability. Examples would be repeated seizures or status, respiratory compromise that requires intubation, ventricular tachycardia that's accompanied by hypertension, cardiac or respiratory arrest, esophageal stricture or DIC.

The category in the middle, the moderate outcomes, are those that are more systemic than the minor effects but are not life threatening or showing any residual manifestations that are persistent. Examples here would be corneal abrasions or acid base disturbances, high fever, disorientation, hypertension that's rapidly responsive to treatment or an isolated seizure.

Table 13 shows that we also capture the duration of clinical effects for each case that's coded as minor, moderate or major, and in Table 15 we'll see a focus on the tox-related interventions. We only capture some therapies that are used, and they tend to focus more on antidotes or things that are specific to toxicology.

If you turn the page to page 460 now on Table 21, and then look down to -- You are here now in the middle of a summary of all the fatal exposures that were reported to this database. Just as an example, I'm going to take you through an acetaminophen therapeutic error so that you can see how to use this information.

It's case Number 180 on page 460. This is an 11-year-old patient who dosed herself with acetaminophen excessively for an ankle sprain, using more than 300 mg per kilogram over 24 hours. In this table, you can get the route of exposure, the reason and, if available, the highest blood level that was reported in the individual case.

If you turn to page 495, you can see an abstract of the case. Now this compendium does not have abstracts for every single case that's listed in every single fatality reported. We only abstracted

about 8-10 percent of the deaths. However, on page 495 at case Number 180, you can see the entire hospital course of this patient and get the idea of how this therapeutic error actually occurred.

Go back to page 485. Here we have a listing of all of the pharmaceutical categories with the number of exposures, the age distribution, the reason distribution, the use of health care facilities, and the outcome, where it's definitive.

Forty-two percent of this database involves pharmaceuticals. If you look at the bottom of page 495, you'll -- sorry, 485 -- you'll see for acetaminophen-only products, you can see for, say, pediatric formulations that in 1996 there were 34,729 cases reported in this database.

Then you can see the breakdown into children by age, the reasons for exposure, the health care facility utilization, and the outcomes for this case.

We've also listed acetaminophen in combination with other substances, in aspirin products, both alone as single ingredient and in combination with other substances.

If you go further down in the table, you'll see the same data for ibuprofen. Ibuprofen

here is separated into OTC, Rx or unknown. If OTC or Rx, these data are inaccurate for ibuprofen. You need to lump them altogether. The OTC versus Rx designation is such a moving target, our database has not been able to keep up with it.

Now if you turn now to this blue handout, there's two points I want to make in here. The first one is on page 9, the top table, Table 3. It shows you a distribution of symptoms, and in this case it's for calcium channel blockers, but the point here was to show that there are about 120 different clinical manifestations captured in this database, and you can characterize and profile an individual drug.

So, for example, you could compare the calcium channel blockers or the analgesics, and get the symptom distribution, either by brand or by product category.

If you turn to Table 12 on page 14, you'll see that each case is actually listed in an outcome log. With the case, the clinical effects are listed, and they're coded, and the coding is -- As you look on this page, you'll see that for this exposure a C7,1 -- C9,1, and this is our compact way of coding.

C7, which is hypotension, and the comma,1 means that the person who handled the call thought it

was related to the exposure. C9, tachycardia, age 3, increased bilirubin, etcetera. So you can go through and get all of the clinical ma nifestations associated with an individual case.

Now in the test database quality control occurs at many levels. We have audits both nationall y and locally within the center. We have rejection of cases with errors and total cases corrected an d resubmitted.

We have required minimum quality factors for each poison center that su bmits data, and we have a review of each fatality in this database by thre e medical toxicologists before it is deemed to b e related to the substance that was implicated; bu t despite our rather persistent efforts, we do offer an unconditional guaranty with this data that the dat a are not perfect.

Test data have been used to support a number of regulatory actions. They were used t o support the change in labeling and packaging of iron. They've been used in applications for OTC switches fo r the NCH, the H2 blockers and nicotine patches.

CPSC uses these data to require chil d resistant closures on dibucaine, lidocaine , acetylnitrol containing products, and ethano l

mouthwashes, and EPA uses them when they re-register or cancel the registration of pesticides.

Now let's use test data to help determine whether pediatric analgesic/antipyretics should be labeled for children under the age of two. If we could turn to the first overhead, please.

This shows the number of exposures to acetaminophen, ibuprofen, and aspirin. The number of exposures roughly parallels the market share or availability in the home and, therefore, the accessibility to a child under the age of six. So the large number of acetaminophen exposures would have been predicted based on - because it reflects acetaminophen's greater market share.

Now I've put cough and cold medications up here, just as a comparison category, and I've sub-selected this set of cough and cold medications that do not contain analgesics/antipyretics. So these are just antihistamines, decongestants, and antitussives that are not formulated with acetaminophen or aspirin or ibuprofen.

The next row gives you the number of therapeutic errors with each of these compounds. That is followed by the percentage of all of the exposures that are therapeutic errors. So you can see that

rate of about 14 percent for acetaminophen, 8.8 percent for ibuprofen, and 2.6 percent for aspirin.

Aspirin data, I think, are somewhat erroneous here. You really have to throw out this therapeutic error rate, as most of the low dose products are actually in use by adults. So it's hard to make as a comparability issue.

I've taken also the therapeutic errors and compared them as a ratio with the pediatric dose equivalents in millions sold in 1996, and you'll see that for acetaminophen it's 1.7, and for ibuprofen 1.05.

There were a total of nine therapeutic errors in the '96 database related to acetaminophen or ibuprofen. Again, all this data is in children under the age of six. Nine of these therapeutic errors with a moderate outcome, three of the therapeutic errors had a major outcome. These were all acetaminophen therapeutic errors.

The first is a 12-month-old who ingested an unknown formulation in repeated exposures over 8-24 hours, had transaminases over 1,000, a prolonged PT, was treated with IV NAC in an intensive care setting, did not receive a transplant.

The second one, a 16-month-old ingested --

Sorry, we don't know the route of exposure, whether this was an ingestion or a rectal use of acetaminophen suppositories, but we do know they were adult strength suppositories; ended up with transaminases over 1,000, a prolonged PT, abdominal pain, was given Pionac and Vitamin K, and no transplant. Now this is all from the database. There aren't the full abstracts of these cases. So there's limited information available.

The final major effect was a 17-month-old with a chronic ingestion over more than three months, had some LFT abnormality that was not a transaminase abnormality, was not specified, was evaluated in an emergency department only, and did not receive treatment in the emergency department. So it's unclear whether this is coded as a major effect, because the problem was persistent over many months.

Okay. If you go to the next overhead, please, this is a graph showing the percent of all therapeutic errors occurring in children under six by age. You can see this clear downward trend for acetaminophen, for aspirin -- sorry, for acetaminophen, for ibuprofen, and for the cough and cold medications, the therapeutic errors occur more frequently in children under the age of two.

So we're looking by age at the percentage of therapeutic errors that occur in children under the age of six, that occurred at that particular age group. This is a pretty dramatic demonstration that the majority of these therapeutic errors are occurring in young children.

Now a couple of points deserve mention here. The first regards the shape of the acetaminophen curve compared to the ibuprofen curve. You'll notice that they are relatively different in the under one-year-olds. This is the blue curve compared to the green curve.

I believe that this reflects the fact that acetaminophen in 1996 had 99 percent of the drops market, and since it's the drops that are primarily used in very young children, there's a more pronounced elevation of the acetaminophen curve in the under one-year-old age group.

Now if you recall also the prior table that showed that there was a higher therapeutic error rate with acetaminophen, although acetaminophen appeared to have a higher therapeutic error rate, this likely reflects the fact that therapeutic errors occur with greater frequency in children under the age of two, and acetaminophen has disproportionately higher

usage in this age range.

Now some of you may be wondering why I put Children's Advil on top of these otherwise generic categories. I selected the data because in 1996 it was not available in a drops formulation, and I was trying to answer the question whether this problem that we're seeing here clearly in children under the age of two was related to the drops formulation or was related to the absence of labeling.

Since Children's Advil follows virtually the same pattern as the other pediatric analgesic/antipyretic exposures, these data suggest that the drop formulation is not the major factor in the increased number of therapeutic errors in very young children.

That leaves us with sort of an absence of other apparent factors, and the finger appears to be left pointing at the absence of dose information on the package label as a likely major cause of the increased rate of therapeutic errors in young kids and kids under the age of two.

Now why is the cough and cold graph there? It's interesting to speculate that the flattening of the cough and cold curve may reflect the absence of labeling information on many of these products for

children under the age of six, rather than under the age of two.

Let's focus on the major and moderate outcomes in cases with therapeutic errors, and see if there's an age pattern in cases with significant outcomes as well. First, let's look at Tylenol drops, infants' Tylenol drops.

Okay. Let's narrow the database down. We start with 282,000 exposures in children -- I'm sorry, in all ages to acetaminophen, single ingredient products over a four-year period. That gets narrowed down to children under the age of six with 153,000 exposures, Children's Tylenol products 82,000, Infants' Tylenol drops at 26,000 exposures. Twenty of those had moderate or major outcomes, and nine of those moderate and major outcomes were therapeutic errors. There were no fatalities with the Infants' Tylenol drops in 1996.

The next slide, the next overhead, looks specifically at these nine therapeutic errors. The first thing that is evident is that, of the nine cases, eight of them are under the age of two, which on the one hand might point to a labeling problem, but on the other hand, is really no surprise at all, because they ask the age in which drops are used.

Remember that it is the age that drops are used, but it's also the age where there are no dosing instructions on the label. So the parent has to guess at the dose or recollect the health professional's advice without any way to check the label to confirm it.

Now looking at the next overhead, at all acetaminophen formulations instead of just drops we see 23 therapeutic errors in children that had moderate outcomes, major outcomes or deaths; and of these, 11 we know involved pediatric formulations exclusively.

Of the 23 therapeutic errors with significant outcomes, 70 percent of them occurred in children under the age of two, again pointing to a problem with labeling.

The two deaths include a case in which the mom treated her child with acetaminophen infant drops, ran out of them, switched to chewables, and finally crushed adult strength acetaminophen in the child's formula, and a second case of a three-year-old treated with extra strength acetaminophen tablets.

Now as you struggle to identify a lower limit for labeling -- in other words, how low to go with a new label -- I just want to be sure you're

aware of the data in the next overhead.

These data with acetaminophen by month show that the therapeutic error problem goes all the way down at pretty much the same rate to the two-month-old point before it starts to drop off. So I think this is a significant issue. We can't get rid of this problem unless we have labeling that goes down into the age where the therapeutic errors are occurring.

Now in November of 1991 the FDA requested data from the American Association of Poison Control Centers on the role of dispensing cups and liquid medication dosing errors. AAPCC conducted an eight-day study in 16 U.S. poison centers, gathering data on 34 therapeutic errors involving dispensing cups.

Based on the population served by the participating poison centers, it was estimated that more than 7,000 dispensing cup related dosing errors are reported to U.S. poison centers each year.

Cough and cold preparations were implicated in 65 percent, acetaminophen elixirs in 18 percent, and three major errors were detected, including teaspoon/tablespoon confusion when reading the label on the cup, which occurred in 47 percent of cases; the assumption that the dispensing cup was the

unit of measure, which occurred in 18 percent of cases; and the assumption that the full dispensing cup was the actual dose, which occurred in another 12 percent of cases.

All three of these errors are likely fueled by the difficulty reading or even noticing that there are markings on the cup. As you consider moving to a dosing dispenser, I must urge FDA to require contrasting, easily read labeling on the dosing dispenser so that the dosing dispenser does not contribute to, rather than decrease, the numbers of dosing errors.

Take a standard dosing cup with raised or imprinted lines. Fill the cup with a liquid, and try to see the gradations on their labels. The presence of obvious gradations on the dispenser may also help dispel the notion that the entire dispenserful is the correct dose.

Now as a Mom, I'd like to make a conclusion here. The failure to provide dosing instructions for children under the age of two does not force the parent to call the pediatrician. Because of diurnal variations in temperature, children usually don't spike during office hours, and if they did, their working parents would not notice or begin

to evaluate the fever until after hours anyway.

The evening, night and weekend availability of pediatricians in the U.S. is at best delayed, and failure to provide a dose does little more than force the parent to guess what the appropriate dose should be.

Thank you.

CHAIRMAN D'AGOSTINO: Thank you. Are there questions from the table?

DR. LOVELL: Could we go back to that graph that you showed -- Could we go back to your graph where you showed the rate of or percentage of therapeutic errors by age, and could you again describe how you used the cough and cold preparations and the difference in the curve, and how that informs us about these other products? That left me confused.

DR. LITOVITZ: Let me -- It was the second overhead, please.

Let me begin by saying that these data are really suggestive. This is not data that's going to prove anything, but it was interesting to me that the acetaminophen and ibuprofen curves really came down a whole lot faster than the cough and cold curve.

The cough and cold curve appears to be much flatter over this entire range. It is my

observation, the majority of the products that were included in this have no labeling below the age of six, and so that, if the problem is attributable to absence of labeling, you would expect to see a more prolonged or flatter cough and cold curve and a more rapid decline in the acetaminophen/ibuprofen curves, because at the age of two you start to have adequate labeling for the parent to confirm the dose.

DR. SILVERMAN: Similar, along the same lines: When I was looking at your data, you seemed to imply that a lot of the errors were the use of adult formulations in young children rather than the recommendation on a child dosing schedule.

So to have formulation under two on infant drops wouldn't do very -- would not be very useful, if you gave a table, and the example given was the person who ran out of the drops. Wouldn't a good recommendation, therefore, be not for use in children on the adult formulations? To me, would seem to cut down a significant number of the overdose, especially the significant ones.

DR. LITOVITZ: I think that that certainly is as a second issue. Now when we did -- The example with the 11-year-old is just an isolated case in our fatality reports. I don't have any numerical data to

show whether that's a common problem, but the one table that did have acetaminophen versus pediatric formulations -- Remember that in the pediatric formulation category -- I'm sorry, adult versus pediatric formulations.

In the pediatric category we have only that which we know to be pediatric. In the other categories everything else is either unknown formulation or adult formulation; but, yes, there clearly is a misuse of adult preparations for children.

CHAIRMAN D'AGOSTINO: Other comments? Yes?

DR. TONG: Dr. Litovitz, will you clarify again for me what you said from age one to two with regards to the ibuprofen drops? What was your suggestion, that this was on an upswing instead of following what we've seen here with acetaminophen?

DR. LITOVITZ: The difference here is predominantly -- You'll notice that the acetaminophen and the ibuprofen graphs have a different shape. Okay? When I look at that, I say, well, it's basically because of the starting point, the under-one-year-olds, and 99 percent of the dosing in under-one-year-olds in 1996 was acetaminophen. It wasn't

ibuprofen.

So because you can't have a therapeuti c error without use, I think the higher usage rate with acetaminophen is related to the higher therapeuti c error rated.

DR. TONG: So I thought you ha d said that there was labeling with the ib uprofen product, and my thought was maybe the labeling did have an impact . But it's not the case?

DR. LITOVITZ: No. I wasn't trying t o imply that there was a difference in labeling. No.

DR. SILVERMAN: One more question. Yo u seem to imply at the end that the inability to obtain medical guidance in the evenin g or on the weekends -- Does your database allow time, and did you look a t that, like were a lot of the errors in the evening s and on weekends, which was the implication of you r last statement?

DR. LITOVITZ: Actually, my last statemen t was prefaced as a Mom's opinion. Okay? My database does allow time, but it is the time of the call to th e poison center. So it's the time that the paren t recognizes the error, not the time that the chil d starts having a problem.

I did not look at that. It would be a n

interesting issue to pursue.

CHAIRMAN D'AGOSTINO: Yes?

DR. LOVELL: I'd like to comment on an apparent discrepancy between your database and the SRS database for ibuprofen.

You report here the data 23,000 unintentional ingestions with ibuprofen and like 8,000 intentional. I think the SRS database would suggest that -- this is in children -- that with ibuprofen that the large majority of them are intentional.

So I was wondering if you could comment on the discrepancies between the two databases.

DR. LITOVITZ: Well, first of all, we consider -- We classify therapeutic errors in the unintentional category. Secondly, the intentionals that you see there are not limited to children. There are of all comers, if you're reading off the annual report. So it's broken down into unintentional versus intentional.

The majority of those intentional exposures are teen and adult exposures.

DR. LOVELL: So your definitions somewhat preclude the distinctions that were made by the SRS group, because you would include a parental therapeutic dosing error and a kid's accidental

ingestion --

DR. LITOVITZ; No, we don't -- The proble m is that what you're looking at there is data that' s only divided into unintentional or intentional o r other adverse reaction. What we separate ar e unintentionals into those where the kids are grazing throu gh the house versus those where it's a therapeutic error or environme ntal cases or bites and stings or food poisoning, etcetera.

So we have a lot of subcategor izations of unintentional. What you saw -- The numbers you sa w here were the actual therapeut ic errors separated out from other exposures. In the under six-year-olds , virtually all of those were unintentional exposures.

So the very first slide that I showed you for ibuprofen, for example, in 1996 had 23,00 0 exposures in children to ibupr ofen. Virtually all of those are unintentional, and another 2,000 -- a subse t of those, 2,000 of those, are therapeutic errors.

CHAIRMAN D'AGOSTINO: Yes?

DR. KODA-KIMBLE: Could you go over again the major toxicities related to acetaminophen? Were those related to the drop -- I mean, the kid' s formulations or were they adult formulations?

DR. LITOVITZ: We know that, of th e

therapeutic errors -- Why don't we put that overhead back up?

Looking at these data, we have 23 significant therapeutic errors from acetaminophen, 11 of which we know to be pediatric formulations. Okay? Some of the others might be pediatric formulations, but 11 we definitively know are pediatric formulations exclusively.

I mean, for example, one of those deaths under the all-formulations involved a pediatric as well as an adult compound. So it was a mixture. So roughly half of the problem, we know -- the significant outcomes, we know, is pediatric, and roughly half of the significant outcomes probably or might have involved adult preparations as well.

CHAIRMAN D'AGOSTINO: Yes, George?

DR. BLEWITT: What was the age breakdown then of those under 11? How many of those were, for instance, under two-year-old, under one -- of the 11?

DR. LITOVITZ: Okay. The slide right before that shows that eight of the nine patients were under the age of 11 -- under the age of two.

DR. BLEWITT: Yes, that's what I thought.

DR. LITOVITZ: One two-year-old and everybody else is under two.

CHAIRMAN D'AGOSTINO: Do you have a further comment, George, on that?

DR. BLEWITT: No.

CHAIRMAN D'AGOSTINO: Are there other comments or questions from the table?

DR. BLEWITT: Could you put the last item on?

DR. LITOVITZ: Now, actually, there are two cases missing here. There are two cases missing here. This is all therapeutic errors from acetaminophen. The other one is Tylenol drops. There are two other children, and they are both two-year-olds, that are missing on that prior table.

So, actually, out of the 11, you've got three two-year-olds and everybody else is under two.

DR. BLEWITT: Oh, okay. Do you have it for the suspension?

DR. LITOVITZ: I don't.

DR. BLEWITT: The next slide says drops.

DR. LITOVITZ: Right.

DR. BLEWITT: This says pediatric formulations. Then the next slide says infant drops.

DR. LITOVITZ: Right, and the other two cases, I honestly don't know whether they were chewables or elixirs.

DR. BLEWITT: Okay. I was just trying to reconcile the numbers. Thank you.

CHAIRMAN D'AGOSTINO: There's a lot of uncertainty, obviously, in the breakdown of the numbers. Any other comments? There's one from the floor who keeps raising his hand. So I'll recognize him. Could you speak into the mike?

DR. ROSA: How well --

CHAIRMAN D'AGOSTINO: Identify yourself, please.

DR. ROSA: Franz Rosa. How well do you pick up hepatic -- major hepatic reactions to acetaminophen in that these don't develop until several days after the acetaminophen is started?

DR. LITOVITZ: Well, you know, obviously, we don't pick them up unless the health professional picks them up and makes the link to acetaminophen or calls us with a hepatotoxic case to ask if there is a toxin that might have caused it.

If we get a case primarily of an acetaminophen exposure that's called to us from home that's an overdose or a therapeutic error or an accidental ingestion, then we do follow those cases until at least the 48-72 hour point when we know that their LFTs are normal, unless the dose ingested was

less than 150mg per kilogram.

So poison centers are relative ly rigorous in their follow-up of acetaminophen exposure cases . We do capture a relatively large percentage o f pediatric severe outcomes and pediatric deaths.

The test database has a great deal o f difficulty and can be faulted for not capturing adult suicidal or even accidental ov erdoses that are severe or fatal with the rigor that i t does in the pediatric setting.

CHAIRMAN D'AGOSTINO: Franz is from th e FDA. Eric, do you have a comment?

DR. BRASS: Yes. Listening to your data and that of the FDA, one is le ft with questions as to the capture rate of the true i ncidents of these types of disorders, and one of the potentially beneficia l side effects of managed care h as been the development of huge information systems that track for all th e major health systems every patient through the system . Every hospitalization now is on computer.

Have you ever -- Has there ever been a n attemp t, to anybody's knowledge, to try to cross - validate any of the spontaneous reporting systems wit h what is known now to occur in major health systems?

So, for example, one could determine how

many hospitalizations occurred in California for overdoses. Then one could ask how many of those were actually reported to a poison control center to see whether or not you're capturing ten percent, 90 percent of the overdoses through this type of -- serious overdoses through this type of system.

DR. LITOVITZ: I'm not aware of any of that having been done with managed care databases. There has been some validation with fatality databases, and that's where we clearly see the difference between the reporting of adult fatalities and pediatric fatalities to the test system.

DR. BRASS: What are those kind of numbers? What percentage of deaths that are coded on death certificates as overdoses had previously been reported to poison control centers?

DR. LITOVITZ: In the adult setting, because you have the pre-hospital arrests and you have the DOA patients, you're running under 25 percent of the fatalities that are actually -- are being captured by poison centers, varying from region to region, depending on the liaisons that the health facilities in the regions have with their poison control center.

The pediatric fatalities -- We actually report a comparable total number of pediatric

overdoses per year compared to the death certificate and medical examiner databases. Interestingly, they are not identical cases. So --

CHAIRMAN D'AGOSTINO: Ted?

DR. TONG: I'd like to take this opportunity to maybe editorialize on two things. Last month this committee sat and discussed the issue of whether to leave poison control centers on labels of over-the-counter medicines, and I think there's a compelling reason to keep poison centers mentioned in the labels for over-the-counter medicines. You can see the data that's collected. It's voluntary, and it's really self-regulated, and I think, you know, presents a good picture, not the entire picture, as I think Dr. Brass was getting at.

The other thing is I know we're talking about analgesics and antipyretics at this point, but in your data 71,000 cases involving colds and cough preparations involving children younger than six years of age in which there were ten deaths and 131 major outcomes or complications.

That might be an issue for a future discussion in terms of, again, information and labeling, because certainly that's over ten percent of your total numbers of cases reported.

DR. LITOVITZ: And also the da ta suggests that the therapeutic error rate with cough and col d medications is roughly twice that with the analgesics .

CHAIRMAN D'AGOSTINO: Are there othe r comments? This is a good time for a break. Why don' t we come back at 10:15.

Dr. Berlin, there is a place a t the table for you.

(Whereupon, the foregoing matt er went off the record at 9:58 a.m. and went back on the record a t 10:15 a.m.)

CHAIRMAN D'AGOSTINO: Dr. Cheston Berlin is now going to speak to us.

DR. BERLIN: Good morning. I'm Chesto n Berlin. I'm University professor of pediatrics a t Penn State University College of Medicine. I'm a practicing pediatrician at the Penn State Guysenge r Health System, and I recently concluded a tour of 11 years on the Committee on Drugs, the last four o f which I served as Chairperson.

I am not here in an official capacity of the American Academy of Pediatrics, but I would like to present to you a distillati on of the thoughts that we've had over the past four years on a number o f labeling issues, and particularly the one that we're

discussing today.

The first statement I want to make is that we are a fever phobic country, and this explains the intense interest we have -- This explains Dr. Litovitz's fantastic database of the reports and explains the large number of unfortunate events that we have associated with antipyretics.

There's only one reason to use antipyretics in children, and that is to make the child more comfortable, and even the data on that is somewhat equivocal in some of the areas used to measure comfort.

The toxicity that we've heard about this morning is almost exclusively in children who have received these for fever and not have received them for pain. I want to make sure that that is an important issue. I think this is because fever imparts a difference to the physiology which may make the patient more at risk for toxicity of the compound.

For at least the last ten years, it is now established practice in pediatrics to give one or the other of these compounds, acetaminophen or ibuprofen, to children down to age two months on a regular basis because of the administration of immunizations.

There is a large number of paper s

attesting to the efficacy of this. Unfortunately, most of those papers are unassociated with pharmacokinetic data, but at least there is some pharmacodynamic data and some safety and toxicity data.

So this is now the reality. We are using these in children down to two months, and we think that appropriate, clearly labeled products will be of really great benefit.

We continue to be somewhat mystified, and I think that our industry colleagues will help clear this up in their presentation, of why there has to be so many different formulations of these compounds, especially two different kinds of liquids. I think that this is a significant problem, and if we could have just simply one liquid with one concentration, things would be much better.

I have long advocated doing away with the term teaspoon. There is a 100 percent error in flatware and cooking teaspoons, and parents will use this, and many of the labels on the products we are talking about today, although they want you to use their calibrated measuring item, they still use the term teaspoon.

So parents grab whatever teaspoon they can

find. It may be a tablespoon, and there are surprisingly a large number of people who really do not know the difference between a teaspoon and a tablespoon.

The labeling is very unclear. I spend a lot of interesting time in pharmacies. I've been questioned a few times by pharmacists of what I am doing there, but I like to read labels, because I learn a lot; and they are occasionally quite opaque.

For example -- and I want to make a special point about suppositories -- there are three different dosage forms of suppositories that I could find. One of them is a 325mg suppository for ages 6-12, and it says one suppository every four to six hours. That would be a maximum of four a day, but then it's followed by the statement, "Do not use more than eight in 24 hours."

Same labeling for a 80mg infant suppository for three to 11 months, one suppository every six hours, do not use more than six in 24 hours. So you can appreciate the kind of confusion that might exist.

I still have patients that refer to these products as liquid aspirin, and I was relieved to see that the number of reports of untoward events from

aspirin remains very, very low , and we have to try to do what we can to dispel this notion that this is a form of aspirin.

Finally, I want to also make a plea that we pay attention to a possible difficulty with prescription drugs that might be used for antipyresis , but more likely are going to be used for pain control , being switched from prescription to over-the-counter status without necessary pediatric labeling or pediatric formulation.

I think I just have -- Can somebody turn the projector on for me, please. I just have three slides I want to show you to illustrate the things that I am talking about. Thank you.

I think we have some actual packages here with us today, but you can see how clustered and crowded this labeling is for most of our patients , 80mg per 0.8ml. I'm not quite sure why we have that. why don't we have 100mg per 1ml, and here is the difference between the labeling between the drops and the liquid.

The only -- You look at this quickly, and you can appreciate that people think this is the same as this. Liquid and drops are really the same, and it's here also, of course, somewhat more difficult to

decipher and to translate. The concentration of this is 150mg per 5ml.

So we have here one, two, three different dosage forms between these two products. The same situation with regard to this particular form of ibuprofen, 50mg per 1.25, which is defined as a dropperful, and here is the suspension. It's not entirely clear why this suspension is different than this suspension, but yet you can see this says 100mg per 5ml, where this, of course, would be 200.

So here we have the same words on a product, but very different concentrations.

Finally, a comment about labeling in general, which continues to be confusing. This added just appeared this year, and it says that they cleaned up the labeling, and it's not quite clear to us why this was done this way, to begin with.

This dosage discrepancy between two different forms of Benadryl was brought to my attention by one of my patients. I don't think there was any professional notification that the new dye-free formula was going to have less, but I was told initially on inquiry that the reason for this was an issue of solubility, and they had to make it one-half of the previous one, and yet now I find that suddenly

the solubility problem has been solved, and we now have 12.5 for both forms, which is good news indeed.

So I'm hoping that we can get some uniformity of labeling, both in terms of the concentration of the suspension and in terms of the information that's on the label.

I continue to make a plea for putting on labels in a prominent position that they may have other ingredients in them. There is a brand name sore throat formula out there that does not have on the front panel that it contains acetaminophen.

So that, if a child is getting acetaminophen for fever and this for sore throat pain, this child is getting a double dose of acetaminophen, and I've calculated out for an average four-year-old that the girl would be getting between 35-40mg per kilo of acetaminophen.

So that's the other area of labeling that we need to have some clarity on.

That concludes my presentation.

CHAIRMAN D'AGOSTINO: Thank you, Dr. Berlin. Are there questions? Comments?

If there aren't any, then let me thank you once again for that presentation, and move on to the next item on the agenda, which is the Nonprescription

Drug Manufacturers Association . Dr. Bill Soller will begin t he discussion, then will, I guess -- Bill , you're going to move from one speaker to the nex t within your agenda?

I've been asked also to deviate form m y usual practice of holding them to the amount of time. Actual ly, we've built up some time now with Dr . Berlin, but there's some issues which we may want to go back to from this morning, also within thi s presentation, and it would be a good opportunity for us.

DR. SOLLER: Thank you. Can y ou hear me? Is this microphone on?

CHAIRMAN D'AGOSTINO: Is it on?

DR. SOLLER: Can you hear me now? I thin k it's on. At least I can hear me echo.

Good morning, Mr. Chairman, members of th e committee. My name is Dr. Bill soller. I'm Senio r Vice President and Director of Science and Technology for the Nonprescription Drug Manufacturer s Ass ociation, NDMA. We are a 116-year-old trad e organization representing the manufacturers an d distributors of nonprescription medicines.

As companies, by sales our member s represent over 95 percent of the over-the-counte r

marketplace, and we have commented on virtually all aspects of the OTC review. In fact, we were here in, I guess, '95. We were presenting to the Nonprescription Drug Advisory Committee, and I think there were seven members that are not here today. So there's been turnover in the committee.

Dr. D'Agostino, if we could take clarifying questions as we go through and, if we have substantial questions, we have time at the end for Q&A.

CHAIRMAN D'AGOSTINO: Fine. I think that's a good approach.

DR. SOLLER: Today's discussion is a subject that is not a subject of a supplemental NDA, is not a subject of a monograph amendment. The scheduling on NDAC's schedule was unexpected for us.

We've had a matter of weeks to prepare, but we think we've put together some useful information which you can use in your deliberations on this particular issue. We have a handout that we have given to you, and it's a blue handout, and we'll be walking through this sequentially.

If I could have the next slide.

With me, presenting today is Dr. Samuel Lesko, Senior Epidemiologist, Slone Epidemiology Unit,

Boston University; Dr. Tony Temple, Executive Director of Medical Affairs, McNeil Consumer Products; and in addition, as part of -- to help with the discussion, we have several other experts with us, including Dr. Ralph Kauffman, Professor of Pediatrics Pharmacology, University of Missouri; Dr. Richard Weisman, Director of Florida Poison Control Information Center, Research Associate Professor of Pediatrics, University of Miami; and Dr. Wayne Snodgrass, Professor of Pediatrics and Pharm Tox, University of Texas Medical Branch, Galveston.

Our remarks are in five parts. I'll start with some introductory remarks, and then we will get into a discussion of the lower age limit, rationale for the liquid and infant drops formulations, our recommendations on pediatric labeling, and packaging and then a summary.

By way of overview, this is follow-up to the January '95 NDAC meeting. Pediatric dosing schedules for analgesic/antipyretics and cough/cold preparations were looked at at that time, particularly the reconciliation of the finely divided age breaks for the analgesic/antipyretics and the age break at age six for the cough/cold.

At the end of the day -- I think it was

the last question -- in looking at what the minimum age should be, the answer from the panel was on a case by case basis. As we've looked at the comparative material that was given to you, we understand that we are really looking at the antipyretic liquid formulations issue.

We're focusing on acetaminophen and ibuprofen, not aspirin which can't be formulated as a liquid as we think about a child that would be dosed under two, and we prefer a liquid; and we're looking at the lower age limit and the benefits of liquids and broths.

Next slide.

By way of looking at the formulations, the drops and liquids -- the drops, obviously, more concentrated. This is the acetaminophen concentration, the ibuprofen concentration being 50mg per 1.25 ml, and the liquid acetaminophen here for ibuprofen is 50mg per 2.50 ml.

The dropper has line demarcations at .8 and .4, and the cup, teaspoon or tsp. demarcations that reconcile with what the dosage directions are, and we'll show that in actual labeling. Drops for two to three-year-olds, although we know it is being used in children under two, as you heard from Dr.

Berlin, and the liquids labeled two-to-six-year-olds.

Just a brief comment on treatment of fever, and a similar comment toward what Dr. Berlin said. The principal source often of viral infection presenting as URI -- Dr. Lesko will have a little bit more to say about this in terms of the Boston fever study.

Fever is often uncomfortable, often associated with other symptoms, other signs such as headaches, malaise, muscle pain, anorexia, irritability, restlessness, poor sleep; but the primary reason to treat a child is not to lower the fever per se. It's for the comfort of the child.

So in sum, we are focusing on acetaminophen and ibuprofen pediatric liquid and drops formulations. We're focusing on this question of what should the lower age limit be, what is the nature and extent of the potential confusion, consumer confusion, if any, between drops and liquid formulations.

As we get into discussing these two questions, just as a side comment here, I found it interesting hearing from Dr. Litovitz today and the FDA presentation and then reflecting on what we were going to be presenting today in terms of the Boston fever study and our adverse experience data that we've

all looked at this in slightly different ways.

I think this gives you a good foundation as you get to the questions later in the day and as we focus on these two questions of the lower age limit and the confusion issue that does exist.

Lower age limit: As we get in to the meat of our presentation, a brief comment on the recommendation and rationale for the lower age limit, and then we will get into a discussion of the supportive data. I'll have a brief comment on established efficacy, and then turn the mike over to Dr. Samuel Lesko, Boston University fever study.

Well, we recommend a lower age limit at least down to six months of age, and we chose this six months for the following reasons: Current pediatric practice; doctors recommend to parents to use fever reducers in children under two years of age for fever, for the immunization schedule, but there is no OTC labeling which, at present, we think, would serve to inform the consumer and reinforce doctor recommendations.

In addition, there is clinically demonstrated safety and efficacy for ibuprofen and acetaminophen down to at least six months of age. Some trials go to two to three, but the Boston fever

study, which was the prospective study, goes to six months, and that's basically in preparation for this meeting where we came to the endpoint in thinking of the lower age limit.

Now you've heard, I believe, from Dr. Berlin that the top side should be lower, and there may be other information that you're hearing today that would suggest that it should be lower than six months, and the industry would support that as well.

Finally, our last reason: An acceptable adverse experience profile so that, as we might capture this in one sentence, the label should not, we think, be silent on information that would be useful for a physician and consumer interaction, given what we know in terms of the safety of acetaminophen and ibuprofen.

A brief comment on efficacy -- well studied for these two ingredients, acetaminophen and ibuprofen, 22 published randomized controlled trials on APAP and ibuprofen for fever reduction in about 3700 kids, two months to twelve years of age, to establish fever reduction in this range, 5-10mg per kilogram ibuprofen, 10-15mg per kilogram acetaminophen, and again another comment.

You were given the Kramer et al. study in

the pack. That looked at 225 febrile children, six months to six years of age, with temperatures at or above 100.4 degrees; 10-15mg per kilo acetaminophen versus placebo, and among the findings significant improvement in activity, alertness, improvement in mood and eating, for treating the comfort of the child.

So with that background, what I would like to do is turn the podium over to Dr. Sam Lesko, who will give you an update of the Boston fever study, and I will comment that in 1995 during the approval of pediatric ibuprofen the Nonprescription Drug Advisory Committee did look at these data, but again seven individuals on that committee are not present today because of the turnover. So Dr. Lesko will walk us through the data and look at the under-two age group that's represented in that database.

Dr. Lesko.

DR. LESKO: Thank you. Can we put the slides up.

What I'd like to do is describe for you the results of a very large, post marketing study of the safety of antipyretic use in children, the study that we call the Boston University Fever Study.

As Bill has already mentioned, I've

previously presented the basic results of the study to this committee in March of 1995, but because the committee composition has changed, I'll review the study design, but will focus most of my remarks this morning on the data as it applies to children under the age of two years.

These results have also been published in The Journal of the American Medical Association and, I believe, were instrumental in the Committee's decision to recommend over-the-counter sales of children's Motrin.

Briefly, the purpose of our study was to assess the risk of rare but serious adverse events following the use of ibuprofen suspension for fever in children. The study was designed and conducted by the Slone Epidemiology Unit of Boston University, was sponsored by McNeil Consumer Products Company, and conducted with guidance provided by a committee of independent experts composed of experts in clinical pharmacology, toxicology, and the relevant pediatric subspecialties.

The study is an office based, randomized, double blind, acetaminophen controlled clinical trial. Patients were enrolled by more than 1700 primary care physicians from throughout the country, and a total of

more than 84,000 children participated in the study.

These children were seen by their physician during an acute care visit, and the primary eligibility criteria for the study were that the child have an acute febrile illness which, in the opinion of the examining physician, warranted treatment with an antipyretic. The age range for children in the study was six months through 12 years.

Eligible children were randomly assigned to receive one of three antipyretic suspensions, either acetaminophen at 12mg per kilo per dose or either or two doses of ibuprofen, 5 or 10mg per kilo per dose.

The primary outcomes for the study were hospitalizations for those conditions associated with ibuprofen use in adults. That is, namely, acute gastrointestinal bleeding, renal failure, anaphylaxis. Because of the recognized association between aspirin use and Reye's Syndrome in children, we included Reye's Syndrome as a primary outcome event as well.

Follow-up data were collected by contact with the parents four weeks after enrollment in the study. Medical records were obtained for all children hospitalized during the course of the study, and it's a review of that medical record information that

provides our outcome data.

The data analysis, simply put, was to compare the hospitalization rates for children treated with acetaminophen compared to those treated with ibuprofen, and the study was conducted between February of 1991 and June of 1993.

Of the more than 84,000 children enrolled in the study, we obtained follow-up information on 27,065 children who were less than two years of age, about 57,000 children two years and older.

The median age for the younger group, the group we're focusing on this morning, is 13 months. The median weight of 10 kilograms, 54 percent were male, and the majority were white.

The cause of fever that we saw in these children is fairly typical of what we would expect to see in pediatric outpatient practices. Upper respiratory tract infection was common in both age groups. Otitis media or ear infection was more common in the younger children than older. Pharyngitis or throat was more common in the older children. Lower respiratory tract infection -- and by that I mean bronchitis and pneumonia -- and gastroenteritis were similarly distributed in the two age categories.

Now not all of the children enrolled in

the study actually received any study medication. Owing to the episodic nature of fever, about five percent of the children overall did not receive the study medication, and a slightly smaller percentage in children under age two. About four percent of these children received none of the study medication.

Of those who have received the study medication, a median of between six and ten doses of medication were received over a median of three days.

If we further stratify the data in either of these age categories according to the specific randomization group -- that is, the specific medication product -- we find that the distributions are dead on equal. So there was effective randomization of the drug assignment within this population.

I'd like to turn now to a review of the outcomes data, and I'm first going to look at hospitalization for any cause during the follow-up period, and on this table I'm showing hospitalizations for children less than two years of age.

Out of 27,000 participants in the study, 385 children were hospitalized, for an overall hospitalization rate of 1.4 percent. The hospitalization rate did not vary by treatment group.

The same proportion of children treated with acetaminophen were hospitalized as were those treated with ibuprofen.

Let me point on this slide, because the next several will be similar, there are twice as many children assigned ibuprofen in the study as acetaminophen, about 9,000 acetaminophen exposed children and nearly 18,000 treated with ibuprofen.

So the overall hospitalization rate did not vary by treatment group. It was, however, about twice as high in the children less than two years of age compared to children two years and older.

If we turn to the primary outcome events for the study, we see that there were very few. Among children younger than two years of age, there were only three children with gastrointestinal bleeding. All of these children had been assigned to treatment with ibuprofen.

Now the three GI bleeds were fairly mild. None of them required surgery or blood transfusion, and all responded to simple supportive expective care.

If we take those three hospitalizations with GI bleeding over a denominator of nearly 18,000 exposed children, we can calculate that the risk of hospitalization with GI bleeding among childre n

treated with ibuprofen is 17 per 100,000.

That risk is not statistically greater than the observed risk of zero in the 9,000 children treated with acetaminophen, nor is the risk of hospitalization with GI bleeding in these data greater among children less than two years of age than children two years and older.

The point estimate for the risk of hospitalization in older children is 2.6 per 100,000, but that is not a statistically significant difference.

For our other outcome events, renal failure, anaphylaxis and Reye's Syndrome, we had no occurrences of those events in either medication group or either age category. So these outcomes were exceedingly rare.

We looked at our data for some other outcome events that might give us some information about adverse consequences of treatment with antipyretics in children, and there are two other diagnoses that occurred sufficiently frequently to warrant an evaluation. Those are hospitalizations for asthma and hospitalizations for gastritis or vomiting.

Among children younger than two years of age, there were 32 children hospitalized with an

asthmatic complication, for an overall hospitalization rate of 118 per 100,000 courses of therapy, and there is no statistically significant difference in the hospitalization rate by antipyretic choice. The hospitalization rate for asthma in children younger than two years is about 90 percent greater than the corresponding rate in children two years and older, however.

I've also showed on this slide children hospitalized for bronchiolitis. Bronchiolitis, as you probably know, is a condition associated with acute wheezing in children, and there's a fair amount of diagnostic confusion, but the distinction between an asthmatic episode and an episode of bronchiolitis may be quite fuzzy in children.

So I've displayed the data for bronchiolitis as well. There were 33 children hospitalized with bronchiolitis, a similar rate to the asthmatic admissions, and again there was no statistically significant difference according to choice of antipyretic.

There were virtually no cases of bronchiolitis in the older children. So an age-specific comparison cannot be done.

For the diagnosis of gastritis or

vomiting, there were only nine children younger than two with that diagnosis. The overall rate was 33 per 100,000, and did not vary significantly by choice of antipyretic. The hospitalization rate for gastritis was also the same in both age categories. That is, it was no more common in the younger children compared to the older children.

Although we did not see -- or did not have any children hospitalized with renal failure, we sought evidence in our data that there might be an effect of antipyretic choice on more mild degrees of impairment in renal function, and similar to an analysis we conducted in the overall study in which we looked at admission creatinine levels in children hospitalized during the course of the study and compared the mean creatinine level on admission according to antipyretic assignment. We repeated that analysis for children younger than two years of age.

In the main study we found no difference in mean creatinine on admission. For children younger than two years of age, we had analyzable creatinine data on 112 children, and among children exposed to acetaminophen the mean admission creatinine was 0.34mg per deciliter. 0.42mg per deciliter was the mean among children treated with ibuprofen.

On a simple unit vary comparison, a simple t test, that difference is statistically significant. The p value is .03. When we conducted a multi-varied analysis using ANOVA, taking into account age, race, weight, and the presence of dehydration, the difference is no longer statistically significant.

We also looked for evidence that an elevated serum creatinine might vary in prevalence between treatment groups. Using a cut point of 0.7mg per deciliter, there were none of the children exposed to acetaminophen that had a creatinine level that high, but six percent of children treated with ibuprofen had a creatinine level at least that high. This, again, does not represent a statistically significant difference, however.

We further explored the creatinine data by looking at age and dose specific categories, reasoning that if this was a causal association, we might expect to see higher creatinine levels in the higher ibuprofen dose group, and we did not see that.

We also considered that, if it was an age specific phenomenon, we might see higher creatinine levels in children under one year of age, and we did not see that either.

So to summarize, what I'd like to say is

that, among 27,000 children less than two years of age, ibuprofen suspension was not associated with an increased risk of hospitalization overall or hospitalization for acute GI bleeding, renal failure, anaphylaxis or Reye's Syndrome, when compared to acetaminophen.

The absolute risk of hospitalization with GI bleeding in these data for children less than two years of age treated with ibuprofen was 17 per 100,000 courses of therapy, and that was not significantly different from the rate observed in children two years and older.

Among children treated with acetaminophen in the study, none was admitted to the hospital for any of the primary outcome events the study was designed to look at, GI bleeding, renal failure, anaphylaxis or Reye's Syndrome.

The higher rates of hospitalization overall and hospitalization for asthma in children younger than two years of age is not unexpected. That's a recognized phenomenon in pediatrics. The observation that, among children younger than two years of age that were hospitalized that we saw this slightly higher mean creatinine on admission to the hospital than the ibuprofen treated group, we think,

has to be viewed with some caution.

That difference is small. The means were essentially within the normal limits for age specific creatinines, and the analysis was conducted post hoc in a setting of multiple comparisons. So that the calculated p value for that univariant comparison is probably an underestimate of the probability that chance accounted for our observations.

With that, I'd like to conclude.

CHAIRMAN D'AGOSTINO: Thank you. Just to make sure we're all saying the same thing, the under-two means six months to two years. Right?

DR. LESKO: That's correct.

CHAIRMAN D'AGOSTINO: The answer is that's correct.

DR. LESKO: That's correct. There may, in fact, be a small number of children in the study who we would calculate an age of five months, but six months is the effective lower limit.

CHAIRMAN D'AGOSTINO: Questions? We can hold the questions to the end. They may be picked up in this next couple of presentations.

DR. SOLLER: Thank you, Dr. Lesko.

What I'd like to do now is to move to review of our adverse experience profile for the

infant drops and children's liquids and, specifically, to look at the NDMA member adverse experience survey that we did in preparation for this meeting, and then a review of selected cases.

We, as I will show, took a slightly different approach than FDA took, because as we were looking at this issue, we wanted to focus down to the issue of teaspoon amounts being used to dose the drops product, and that's what we're going to show you here.

The purpose of our survey was to review spontaneous OTC adverse experience reports to companies, to help assess the safety and define the nature and extent of potential confusion, if any, with the drops and liquid formulations.

It's just a comment in terms of the differences between the FDA review and the NDMA review of adverse experience, not to say one is necessarily better than the other; but as I said earlier in my comments, provide interesting perspectives.

The FDA review looked at all products, including the solids and all the different liquids back to '69 in the materials that were given you, no denominator estimate, including all reports of suicide and so on.

We looked at the OTC liquids and drops.

We looked at the last five years, '92 to '97, and you'll see through this that for ibuprofen we're basically talking about '95 through '97. It's somewhere between a year and a half to two years of experience.

The reason we took that is so that we could get a denominator estimate. Our sales records in terms of units shipped go back five years, and that's where we have accurate records. So we decided to focus in on those last five years, and to focus in on the issue of using teaspoon amounts for the drops.

We have five companies, representing over 90 percent of the OTC children's/infants single ingredient, liquid and drops, fever reducer, pain reliever market, all five of the major OTC brand name products, over 75 percent of the store brand products over this period of January 1, '92 through June 30, '97.

Just a couple of points to consider: The first has to do with how we define serious, as you go through this, both in our review of the NDMA member survey as well as what Dr. Temple will show you, and just to review from the MedWatch definitions: Death, life threatening, hospitalization, disability, congenital anomaly, and requiring intervention to

prevent permanent impairment or damage -- the shorthand for a longer description of that.

The second has to do with several caveats, and you've heard also some caveats in the FDA presentation. We cannot develop concurrent incidences from these data. The reason is that there is underreporting of adverse experiences in general. The second is causality cannot be inferred. All reports are submitted by a company if the drug is reported in the record.

Could I have the next slide?

This is from the Code of Federal Regulations on requirements for records and reports concerning adverse drug experiences, only to point out a disclaimer in Section G that, if there's not a report going -- a report going in does not necessarily reflect that the reporter of information constitutes an admission that the drug caused or contributed to an adverse effect.

Just a brief comment before we go back to the previous slide, and that is that you've heard earlier that 23 percent fatality with acetaminophen, and that was the phrase used. We cannot -- What that really meant was there was a 23 percent -- I'll call it a rate, but it's not a population rate -- within

the adverse experience database that was reported . this is not a 23 percent that is a population rate , and that's part of the point that we're trying t o convey here, because of the limitations that we have with adverse experience reports.

Previous slide.

The next point is: As we are looking at the denominator, we will provide sales data based on units shipped. This is our best estimate. It means it's not doses consumed, but we do present this , because it provides a perspective on the overal l denominator, another reason wh y we can't come up with a population rate.

Then, finally, remember that, as we'r e lookin g at units shipped, we're not talking abou t equivalent pediatric doses; and as you look at units shipped, the children's liquids in comparison to the infant drops are sold in large r volume. So there's a greater number of potential ex posures per unit liquid for mulation. Just a caveat as you look at thes e numbers.

This is an overview of the OT C acetaminophen, ibuprofen NMDA member advers e expe rience survey covering '92 to '97 for childre n under 12 years of age for thos e products marketed for

children up to 12 years of age.

Here we have the formulations broken out for acetaminophen, again a five-year experience, and ibuprofen, a two-year experience broken out for the drops and liquids for nonserious and serious AE. The number of deaths here are from the serious numbers. So death is counted as a serious AE. We broke them out separately here, and over here are the number of units shipped.

Again, you can see an extensive exposure over this period, two children in terms of these products. In addition, you can see for the drops and liquids for acetaminophen a breakout of 13 and 17; for ibuprofen over this period zero and 15, but recognizing this difference in terms of the perspective of the relative exposure to kids.

I would also like to point out that there were two deaths for the drops, acetaminophen, reported, and two deaths reported for the liquid ibuprofen. What I would like to do is just to briefly review these four deaths for you, because we do not believe that they are related to the basic issue of teaspoon amounts for the drops product.

Then what we'll do is I'll turn the microphone over to Tony Temple who will review the

McNeil database which represents the majority of these, because they have the majority of the market, and it is a confined system.

They can look exactly at 1-800 number in terms of what people are asking about these products, but that's instructive, as well as the McNeil database on adverse experiences as we look specifically at the issue of teaspoon amounts for the drops product.

Looking at the fatalities, there were four, two for acetaminophen -- not much information available on these. It was a four-month-old. The correct dose was given. The child died of fatty liver, reminiscent of an inborn error of metabolism or Reye's Syndrome. It was not diagnosed as that, but not characteristic of acetaminophen toxicity.

The seven-month-old was a therapeutic overdose; a Laotian parent unable to read English, unable to read the label, used the dosage amount that she was familiar with in terms of her country of origin.

Ibuprofen: A child 1.9 years, one dose, aspiration, confounded by enzyme deficiency, congenital anomalies and other sicknesses; and a 25-month-old reported to die of anaphylaxis.

So in conclusion, we think the adverse

experience member survey that we compiled supports the results of the perspective study that Lesko presented, and what I'd like to do is to turn it over to Dr. Temple, who will review the nonserious and actually serious cases relating to this issue of product advice confusion.

DR. TEMPLE: Well, I'm happy to be here once again with this committee, and I appreciate the opportunity to discuss these issues. I think you all pretty much know, I'm an advocate for standardizing pediatric dosing schedules, and that would include availability of those schedules on OTC products under age two.

What I want to do is show you some McNeil Consumer Products Company pediatric analgesic/antipyretic data. These are trends in inquiries and adverse event reports that have come to McNeil, and these data are included in the member AE survey that Bill Soller has just shown you, but we'll be able to give you some additional detail at this point.

We're going to talk about McNeil Consumer Products Customer Response Center contacts. What we mean by that is we get letters or inquiries, mostly phone calls by a large number, and we're going to look

at between 1992 to July of 1997, children's liquids and infant products.

We'll focus on how many inquiries, but specifically were there inquiries about dosing, and then were there adverse event reports, which we'll show you the number of, and how many times was the teaspoon used for infant drops. That's what we want to show you at this point.

Now for those of you who aren't familiar -- let's make sure those are well up on the -- so that people -- That's good. For those of you who are perhaps not fully aware, in the OTC industry there may or may not be a requirement to collect adverse event information and report it, because OTC products don't necessarily have that requirement.

Because acetaminophen is an NDA product and has been since 1955, the data are reported, and so the data we're talking about here have been reported to FDA, and I will point out when we talk about specific cases that you've already seen some of these today in the FDA presentation.

When an 800 number phone call or letter comes in, it goes first to Consumer Affairs. They sort out the difference between inquiries about the product, just comments about the product, and then if

there's an adverse event, it goes to the Medical Department for evaluation and analysis and submission to FDA.

Between 1992 and 1997, for all contexts, for all products, McNeil received over 759,000 contacts. That means calls or letters. 71,000 of those were about pediatric analgesic/antipyretic products, and nearly 56,000 of those were about children's liquids or infant's drops, the products we're primarily focused on today.

Of those, 53,654 were inquiries, and 2325 were adverse event reports. Next.

Go give us some perspective then on -- first on the inquiries, and then we'll look at the AEs. Among the 53,000+ inquiries that we received about children's liquids and infant drops over that five-plus year period of time, nearly 5500 of those were dosing inquiries, and the best we can we try to code what the nature of those inquiries are.

Many of these are not age-specific or they are questions about things like can we use two products at the same time, particularly the alternating dosing issue between the two different forms in the marketplace; how do we convert from milliliters to teaspoons, etcetera; but where we could

identify data about age-specificity, what you see is that we have 2530 calls asking about dosing for children under age two, compared to 351 calls about dosing for children 2 to 11.

That seems to be no surprise to us, of course, since people can get the dosing for children ages 2 to 11 from the package labeling. They cannot get it for children under age two, but the fact is that nearly half of all the dosing inquiries that we receive are about how to dose kids under age two.

Many more could be, in fact. We just could not identify that that's exactly what they were about.

The other question is how many questions do we get about whether to use a dropper or a teaspoon or a dosing cup for a product other than for which it is intended. We had 110 inquiries about that. 104 times somebody asked about use of a dropper for the children's liquids, and these are usually circumstances where the parent already has the infant drops, has a dropper in the home. They've run out of drops. Now they go buy the elixir, but they like using the dropper. It's easy to administer to a small child. They want to continue to administer it that way. Can they use the dropper with the liqui

product.

Of course, we tell them that's not the right way to do it, to use the right product for the right dosing device, but that seems to be the most frequent call about this issue.

We did receive six calls asking how to measure teaspoon amounts for infant drops. We had no questions about whether to use the dosing cup that comes with the product for administering infant drops during this period of time. That's a lot of inquiries, a few about these issues.

Now let's turn to the adverse event reports. Several things probably to put this into perspective: First of all, a couple of slides ago I gave you 5325, and there's some of you here who would like to match exact numbers and to see if these numbers add up.

They don't exactly. There were about 50 of those that involved adolescents or adults using the liquid products, and those are not included here. We're really talking about children now rather than just reports of adverse events.

The kinds of numbers we're talking about are over different time frames. For acetaminophen we're reporting 1992 to 1997, because that's the

period of time for which NDMA did their survey, and acetaminophen was in the marketplace that entire time.

I pointed out earlier it was first approved as a liquid in 1955 prescription, and drops in '57, and OTC in '59. So both of them OTC in '59, but we're only looking at the period of time from '92 to '97.

Then for ibuprofen, we're looking at the period of time from '95 to '97. Now children's ibuprofen products were approved as prescription products in 1989, OTC in June of '95. So it's really basically just two years for the liquids, and the drops were approved in June of '96. So it's about one year for the drops product.

So during that period of time we have a much larger database to draw from for acetaminophen. We estimate about 4.7 billion doses shipped. Bill showed you packages shipped. You can -- There's that difference in there -- versus 300 million doses shipped for the two. Okay.

Now for acetaminophen there were 1329 nonserious reports during that period of time, of which nine involved somebody saying that they used a teaspoon to administer infant drops, and we're going to talk about those cases so you can see what they're

about.

There were 30 serious adverse events reported during that period of time, of which two involved teaspoon use for infant drops, and we're going to focus primarily on those.

For ibuprofen there were only -- Well, there were 900 nonserious adverse events reported, but only three that involved teaspoon use for infant drops. That's, of course, over a much shorter time frame, but there were none serious in that category, though there were 13 serious adverse events for this.

Okay. Next slide. This is sort of the heart of what our experience is. These are the adverse event reports, acetaminophen 1992 to 1997, the 11 total cases where teaspoons were used to administer infant drops, as reported to us.

We've arranged these not by year but by age, so you could get some perspective on the age of the child involved. You see that the youngest child is two months. The oldest child was two and a half years, and you can see the ranges as they go up.

This is the reported dose. This is what a parent said. For example, they were told to give a quarter of a teaspoonful. They gave one dose, and that's for one day. So that's just a single dose

excessive dose.

Here is one teaspoonful given as drops . They gave four to six doses a day over two to three days. Here is one teaspoonful given every four hours over about a four-day period. So that's what you see up there.

If you tried to summarize this , the range of dosage administration here ranges anywhere from two to eight times of the recommended daily dose in terms of milligram amounts when the drops were given in these volumes.

In this particular case, this nine-month-old, it was approximately five to eight times the recommended daily dose. It depends on whether you use four or six doses a day that was given. In this particular child it was five times the recommended dose, and in this child it was approximately three times the recommended dose -- I'm sorry, that one right there.

Now the two children identified here, the 14-month-old and the 19-month old, are the two that were labeled as serious. They were both hospitalized . This one is the one you saw earlier that FDA reported . This is a child who was given a teaspoon -- who was told to give a teaspoonful of Tylenol and used drops

instead of elixir, used up about four bottles worth and over a period of time, and did have a liver transplant, recovered.

That's also the case that you've probably heard most of the publicity about, if you've been looking at any recent publicity.

This other case, the 19-month-old, received a teaspoon, got four doses which amounted to a little over 160mg per kilogram, reported that to their physician. The physician recognized that it was in excess of the threshold level for taking action of 150mg per kilogram, hospitalized the child, had them receive acetylcysteine.

The child did not have symptoms of toxicity, and no liver function test abnormalities developed, but because the child was given NAC, it's not certain whether they would or would not have developed toxicity. This was a threefold dose. This was a fivefold dose.

Now we did have this one five- to eightfold dose. The rest of them basically had no symptoms. One reported they had an upset stomach and vomited, and another preexisting stomatitis. So if you look at the actual adverse event reported, it will say stomatitis.

So that's the experience here. What really is striking to me is that most of these cases are under age two. Nine out of the 11 cases involve children under age two where there is not currently dosing instructions on the label.

Let's look at the next one, because even though we have limited experience for ibuprofen, because it's relatively new, we only have three cases where teaspoons were used for infant drops. Two of the three cases also were under age two, one three-year-old.

In this particular case they were given doses approximately twice the recommended daily dose, and the events we considered to be nonserious, limited outcomes, a little diarrhea, upset stomach, some drowsiness. This seven-month-old is the case that was presented by FDA this morning also in that database.

Okay. That basically provides you with the detail in our database to give you what I think is a different perspective, a different look at the same data; but I hope it provides you some -- a better perspective.

Forty-six percent of the dosing inquiries we receive involve asking for dosing information for children under age two. These AE reports, five and a

half years for APAP, two years for IBU, 5 billion doses shipped, 14 reports involve teaspoon amounts of infant drops. Not a large number of cases like this reported to us, but nonetheless, there were two reports of serious outcomes, I think enough for us to at least consider how we can do something about this, and 11 of 14 AE reports used teaspoon amounts.

Where they were using teaspoon amounts in children were children under age two. I think a lot of people have said that. I just want to reemphasize it. This is clearly an area where we think then that adding dosing directions offers a significant benefit for consumers.

Whether it's a first time mother with a first time fever or whether it's a parent who's had many children and lots of experience with treating fevers, we think that the availability of the correct dose at every use is the right thing to do.

We think that, not only that, there's the ability to reinforce or validate health professional instructions if that dosing is on the label.

Thank you.

DR. SOLLER: Thank you, Tony. What I'd like to do now is to turn to our concluding remarks and our recommendations on labeling and packaging.

I'll start by a brief commenta ry on the rationale for drops and liquids, follow that by the specifi c recommendations for pediatric labeling and packaging for OTC products, and a brief summary.

Next overhead.

In terms of the drops and liquids, it' s not just convenience. It's successfully administerin g the dose. For drops, infants have difficulty sipping from a cup, easier placement of the drop in the side of the mouth or on the top, and the volume is smaller . It's not an ml. for a six-to-12-month old. So on e squirt, easier to swallow without aspiration or loss from overflow from the mouth.

With kids, older children use cups . Childr en move from dropper to cup. They need a transition delivery system. In terms of viscosity th e difference in the drops and the liquids, the thinner soluti on is easier to pour, especially when you ar e giving somewhat large volumes.

We also think there is a benef it in terms of potential enhanced accuracy, because with a les s concentrated liquid, as you're dosing in large r volumes, you have less chance for error; and finally, the less concentrated suspensi ons are more palatable, especially when the child is t aking multiple sips out

of a cup.

In terms of our recommendations for pediatric labeling and packaging, I'm going to first talk about the recommended dosage schedule, then specific elements for additional labeling and packaging, and I'll conclude in terms of how putting all these elements together can help in the discrimination between product types.

Well, here we have acetaminophen and ibuprofen. This is the established dose range that I mentioned earlier, 10-15mg per kilo, 5-10mg per kilo, and this is the concentration of the drops and the liquid shown here for acetaminophen and ibuprofen.

We have the age breaks and, if you start from two to three years of age, and this 24-25, this is what is currently on OTC labeling. We have four months here in this particular slide. There's a footnote here. We have come into this meeting recommending dosing down to at least six months of age.

This four months here reflects the four-month age that's been recommended as a lower age limit in professional labeling schedules that have been put out by companies to help professionals.

This column shows the drops and liquids,

dropperful amounts for ibuprofen and acetaminophen and cup in terms of the tsp demarcation on the cup for ibuprofen and acetaminophen, and there are two points that I want to make here.

The first is that we would recommend that, in terms of the unit change as you ascend in weight or age, that they be similar for ibuprofen and acetaminophen for the drops product, and be similar for ibuprofen and acetaminophen for the liquids product.

The second point I want to make is that FDA does have approved dosage ranges, the 5-10mg per kilogram for ibuprofen, and 10-15mg per kilogram for acetaminophen. For ibuprofen it goes down to two years of age, and for the prescription product down to six months of age under the NDA and, of course, there's a tentative final monograph for acetaminophen that recommends OTC down to two years of age, but there is no Rx dosing schedule that is demarcated with age breaks or weight breaks as we're showing here.

So providing this type of schedule, we think, would fill this particular gap. We don't think the label should be silent any longer in terms of information that could be useful to the health professional as well as the consumer.

I'd like to turn now to specif ic elements of the additional labeling -- in terms of additional labeling and packaging that we're recommending. W e have five points.

We think there should be the continue d availa bility of OTC drops and liquids. Next slide . We think that the dropper and the cup should b e calibrated, required to be cal ibrated, for the single ingredient OTC antipyretics and analgesics, and they should be required to be in the box for eac h particular product.

Now it's our understanding, in reviewing the members, that we think all members, certainly all the major brands, are reviewing this for anecdota l reports in the marketplace, that there are som e products where that is not the case. We think tha t shou ld be required, and it would bring, certainly , uniformity across the NDA monograph products as well as across the marketplace.

Third, we think there should b e established standard elements of directions of use fo r NDA and monographed OTC analge sic/antipyretics. Next slide. I'd like to run through these.

Specifically, we think there s hould be an itemized numerical list under the directions of us e

for the NDA monograph single ingredien t antipyretic/analgesics, depending upon th e formul ation, possibly -- some have this; not all o r not all need it -- but "shake well before use," i f that's needed from a formulation standpoint, an d instructions for use, the chart, use weight, i f possible. If not, then use the age listing , instructions to use the enclosed measuring cup , instruction on hourly and dail y dosing, and finally a standardized table format for the schedule where the standardized table heading tha t would be on the order of dosing chart, use only enclosed -- and I have the bracke ts here -- device. It would be "use onl y enclosed cup" or "use only enclosed dropper."

Next. Now this is found in yo ur handout, and I will also be referring to Section 6 later, whic h is a mock-up label that we've done. This particular portio n is for acetaminophen drops. This is a n example of directions for use that might be created, thinking about FDA's proposed new format for th e information panel.

Here we have "Shake well before use. Fin d the right dose in the chart below. Use the weight's dose. Otherwise, use age. Use only the enclose d dropper to dose. Do not use with any other dosin g

devices. Repeat every four. Do not use more than five times a day."

Again, the standardized heading here, a dosing chart, "Use only the enclosed dropper" and then optionally a direction on how to use the dropper and, depending upon the formulation and the specifics of how it's presented, if it's a dropper that is presented alongside of the bottle that has a separate cap and instruction to replace the original cap to maintain child resistance.

Moving on to 4, we would recommend the use with an icon of the dosing device on the principal display panel. Could I have the next overhead? Here is the example of three products. This is the drops. This is a liquid, and here we have a suspension liquid.

These two products, which come from the same company, have the dosing device, the cup here and the dosing device, the dropper prominently, the shape displayed on the panel, and this store brand here does not have that, and we think that would be an added feature in terms of helping discrimination between products.

Finally -- and although I've mentioned consuming here, on reflection I think this is more of

a health professional problem and harkens back to some comments that I made on July 14th to the Nonprescription Drug Advisory Committee on OTC labeling, but we also think that there should be support for the recently proposed label format for active ingredients with the milligrams per dosage units, however that's expressed, but the milligrams per dosage unit as a concept would be first on the information panel.

This is a mock-up label. It's down in Section 6 of the blue handout that we gave you. Just as a caveat, this is not a label that currently exists on the marketplace. However, it was constructed using many, if not most, of the elements that FDA has proposed in the February 1997 Federal Register OTC label content and format, and there are several other things that we've, obviously, added in, as we've thought about this particular issue.

The last point on our recommendations related to the active ingredient with the milligram per dosage first, and that was here and here, first on the information panel. We think that this is important for the consumer in terms of helping to educate the consumer what these products are for and making product comparisons in terms of self-selection,

but this is probably more of a medication error issue.

This is probably more of a health professional issue in terms of providing this information in this place uniformly so that, when a mother is calling the pediatric office and is speaking to the triage nurse and she says, well, turn it over and read to me what you have on that information panel, it is right there in a uniform place; or if it's a poison control call, it can have this information that can be conveyed very easily over the phone.

So as I say, that last recommendation really reflects more of a medication error, more of a health professional to consumer interaction as opposed to perhaps what might be a consumer preference of what they would like to have first on the label.

Just moving on briefly, this is the dosing direction that I showed you earlier, again reflecting "use only enclosed dropper to dose; do not use with any other dosing device," and then a comment on this heading: "Use only the enclosed dropper."

Again, these products are used multiple times during the course of use in the household out of the medicine cabinet, and it is most likely that, as a parent would come back to dose, that they will move

to this section. Having read the label, they will move to this for the second, third and fourth, whatever, dose or maybe the next episode, and reflecting "Use only enclosed dropper" within the title of that table, we think, would be important as well.

This is the grape flavor of that prototype, the same points to be made. We don't need to go through this.

So in summary for the recommendations, continued availability of the drops and liquids for the reasons that we've given, and reflecting the information that we've provided on the safety of the products; requiring a calibrated dosing device for all single ingredient antipyretic/analgesic liquids and drops; establishing standard elements within the directions of use; recommending use of an icon of the dosing device on the PDP, the principal display panel, and then supporting this last issue that we went into in terms of active ingredient first on the information panel.

I'd like to turn now briefly to think about how this might look in the marketplace, and I have a listing of the discriminating elements that would be obtained with this kind of approach.

Of course, the size and shape of the box and the bottle are distinguishing unto themselves, the dosing devices as well. Icons on the dosing device on the PDP, helpful to discriminate between the two. Product identification, brand name, whether it's Advil, Tylenol, infant drops or children's Tylenol, children's Advil, infant -- rather liquid suspension.

Standardized directions of use, the numerical list, the table with the standard heading, icons of the devices on the PDP, and again the active ingredient and milligram dosing first on the information panel, and we know that some companies also add in :concentrated" for the drops as an additional discriminating feature.

So in summary, acetaminophen and ibuprofen, excellent safety records for the liquids and drops; the clinical data, abstract of information that we provided as well as the market experience, the information that we gather support pediatric practice recommendations for an lower OTC age limit, we think, of at least six months for label directions for both ingredients.

The additional packaging and labeling recommendations that we have, we think, are a comprehensive approach. They provide a cohort of

discriminatory elements to the label. It will bring consistency to the marketplace in terms of the NDA and monograph products, and also reflecting on the dosing schedules we've showed for acetaminophen and ibuprofen, all in a consumer friendly format, standard elements in the directions of use, the table, the numerical list, the icons and so on.

So what should be the lower age limit? At least down to six months, and I put this slide in just to reflect again what we're talking about is this example: A parent with a 12-month-old, say, who's at the doctor's office or maybe communicating over the telephone with a triage nurse, gets a recommendation for dosing an OTC fever reducer, purchases the product or has it at home, and then with the new labeling would be able to confirm or even question health professional advice on the dosing.

In terms of the benefits of dual availability of a liquid and drops with the overlapping dosage schedules, remembering the basic safety of the acetaminophen and ibuprofen, the overlapping schedules would provide clear directions to the parent on the appropriate use of both of these products.

They would meet the administratio n

requirements of the infants, the sip and the -- excuse me, we tend to suck liquids, and the children who sip, and they would allow parents to purchase one product to treat children of different ages who are sick simultaneously.

What this comes down to is we think the consumer is better off with more information rather than less information.

What I'd like to do now is to turn this over to Q&A, Dr. D'Agostino, with Dr. Kauffman, Dr. Lesko, Dr. Snodgrass, Dr. Temple and Dr. Weisman available for Q&A.

CHAIRMAN D'AGOSTINO: Weisman is not making a presentation?

DR. SOLLER: No.

CHAIRMAN D'AGOSTINO: Eric, why don't you begin?

DR. BRASS: Since Dr. Soller is at the podium, I have a couple of questions, and most of them have to do with the utility and interpretability of the tables.

If I look at the table you have in your mock-up --

DR. SOLLER: I'm listening. I'm getting the book.

DR. BRASS: -- that you showed as a slide in Section 6, as I look at it, I'm reminded by a recent article in the late press that surveyed what percentage of high school graduates could read a bus schedule, and the number was, as all such stories are, quite embarrassing.

Therefore, when I extrapolate that kind of data to looking at the table you have on your mock-up, I'm concerned at its complexity and interpretability. For example, if I look at the righthand column, the information in parentheses goes from .8ml, then the next line is .8+0.4 --

CHAIRMAN D'AGOSTINO: Can that be put up?

DR. BRASS: Yes, there was a slide of that.

CHAIRMAN D'AGOSTINO: Yes, it might be helpful so the audience can see what we're referring to.

DR. BRASS: No, I understand it. Then two times 0.8 with the dropper number. Again, do you have any information as to how consumers will use a table constructed like this?

DR. SOLLER: We don't have any specific information, to my knowledge, in terms of label comprehension studies, and I don't know whether there

were any done by the company in terms of the approval of the pediatric ibuprofen; but let me comment in two fashions.

Number one, we are talking about the concept here of standardizing in an interpretable way. We're together on that.

DR. BRASS: Right.

DR. SOLLER: I don't have the information to say, yes, 80 percent understand it, but I would also say, reflect on some of the information that you've seen today, because this is basically the schedule that's out there with the vast majority of products.

Tony, do you have anything to add on that?

DR. TEMPLE: My only comment is that you're looking at the larger table. This is consistent with really what's on the label, rather than saying .8+.4.

DR. BRASS: Well, that's what I was trying to get a sense of.

DR. TEMPLE: This is what's currently there. This was just a way of helping people add up in their head, but that's currently what's out there, and our experience is that people know how to use these.

DR. BRASS: Again, that's in terms of our answering the questions that have been posed to us by the FDA. Any information as to what labeling structures work would obviously be very helpful.

I have a couple of questions for Dr. Temple, if I might, and again I am not a pediatrician.

Clearly, the products are being used by consumers with children under age two. Based on either the calls to your hotline -- your 800 number or calls to -- or the adverse event reports, do you know where consumers are actually getting the information they use to dose children under two currently? Are they consulting physicians? Are they extrapolating? Are they guessing? What are they actually doing?

DR. TEMPLE: I don't think I can tell you specifically from our data where they're getting the information. Do they call us to get the information? Our experience is that they usually call their physician, but then they try to remember after that, and they need to be able to have reference information for subsequent use.

I think at least a portion of the time, they are trying to remember what they were told before.

DR. BRASS: And along the same -- the

differentiation between age and weight in dosing, experience as to how consumers resolve discrepancies in the two columns. Do they use weight preferentially to age or do they always use age?

DR. TEMPLE: You know, originally labeling for these products had only age breaks, and it's only been in recent times that recommendations around the use of weight breaks have been there. The rationale for that has been that you can provide a slightly tighter dosing schedule by using the weight breaks.

These weight breaks don't exactly match the age breaks. That was our long discussion in January 1995, and I brought all my slides for that, but I'm not going to show any.

DR. SOLLER: He can speak at 60 words a minute.

DR. TEMPLE: But our experience now is that by putting on the label "use weight, if possible," they will look and see what the weight is. If they don't know the weight, we say use age. In fact, either one is largely interchangeable in terms of the dose they get. There's not that much discrimination between the actual doses they get, either way.

DR. BRASS: Thank you.

CHAIRMAN D'AGOSTINO: Earl?

DR. SILVERMAN: Similar question: When weight is the preference over age, why does age appear before weight? I would have thought that, if you want people to look at weight first, it should appear on the lefthand column rather than the center.

As I look at this, I would read initially, well, if I have a six-month-old, well, I'll probably give him one rather than reading the weight first.

DR. TEMPLE: I'm not sure there's a specific reason for that. I understand that right now only age is available through the monograph as part of the label. I think I have that right. So we're tending to go with the standard format first, offering the weight as an alternative. Down the road, it could be reversed.

DR. SILVERMAN: You are recommending weight being the primary one on your label, and now you're just confusing people. I mean, that's part of my -- The issue here is I think there's some confusion. If you say somebody should go by weight -- if possible, use weight to dose; otherwise, use age. That's what I have in front of me.

DR. SOLLER: Let me offer a perspective, if I can. As Tony had mentioned, we started out with

age breaks, and then there was a move to the weigh t breaks, and I think that gives you the left to right, you know, question culture of how we develop things.

I think, in terms of finding the dose on the chart below, as the person is walking through the directions to say whether one is before the other, an d I don't think we have a particular strong opinion tha t one should be before the other; but I am conveying a couple of points to consider as you come to you r deliberations on this.

If possible, use weight first; otherwise, age. Get that piece of information, and then the y start using the chart and looking at age and weight. Okay? My feeling is most people will look -- afte r reading that, they will look at the weight, whethe r it's on the left or right. I don't personally think that that's going to be much of an issue, one way or the other, but again we don't have the specifics o n that kind of nuance.

DR. SILVERMAN; And can I just ask Dr . Lesko a question then.

When I was looking over your data and you r primary outcomes were hospitalizations for G I bleeding. Well, a common side effect, certainly, of ibuprofen is not -- is vomiting and gastritis ove r

bleeding.

When I added up the numbers, if I'm right, there were nine -- I'm sorry, ten adverse events requiring hospitalization for gastritis and vomiting for ibuprofen versus only two for acetaminophen, when you add up GI bleeding plus vomiting and gastritis.

Have you analyzed the data taking that endpoint, and why did you not include gastritis in the adverse event cause of hospitalization?

DR. LESKO: I don't think it's fair to add the data that way. The three GI bleeds -- two of them had been vomiting prior to their bleeding. So they would have gotten the label of vomiting and maybe recounted in the vomiting/gastritis category. So we can't -- Those are not mutually exclusive categories. We can't simply add them in that way.

DR. SILVERMAN; Yes, but it's not hard to have a hierarchal system. I mean, one can examine the data and look at it, but I'm not sure why gastritis was eliminated, gastritis being far more common, and a serious complication, of ibuprofen versus GI bleeding, requiring hospitalization.

DR. LESKO: Well, gastritis was included in the analysis that I presented here. It was not included under the primary outcome events a priori

when we designed the study.

DR. SILVERMAN: That's my question. Why?

DR. LESKO: Because GI bleeding was the more serious event that we were designing the study to make sure we captured all of those events. That's the reason. We captured information on gastritis. You're right. Gastritis was more common than hospitalization for GI bleeding. We present that data in 1995 and again today.

DR. SILVERMAN: One more question along those lines. When you talk about creatinine levels, differences between the two groups, and you say when you do your multi-variate analysis and you put in dehydration, again similarly, dehydration is going to be -- could be a side effect of the medication secondary to vomiting.

So when you do your analysis and eliminate dehydration, it's not an independent variable. That's my only comment on that.

DR. LESKO: Well, when we look at the creatinine levels in our original presentation in 1995, we focused on children who were dehydrated. We felt that the exposure to dehydration would place these children at the greatest risk, and we saw no difference by medication in that category.

We then subsequently analyzed the data collecting all cases, found no differences in all children, regardless of whether they were dehydrated or not, in the entire dataset. We've replicated that analysis in children under age two, and there is no difference in the creatinine levels, regardless of hydration status, as reflected by discharge diagnoses.

So that dehydration, while it was included in the multi-variate model in one form of the model and not in another, it is included there for a reassurance that we've taken it into account, but when we look at the means, there is no difference by dehydration status.

CHAIRMAN D'AGOSTINO: Dr. Pucino.

DR. PUCINO: Yes. For Dr. Lesko again: The question on the fever study is how much education -- First of all, how much education did the parents have in regards to how to dose; and in terms of the adverse effects, were any of those related to noncompliance with dosing?

DR. LESKO: Let me try to answer the second question first. For the principal outcome events that we saw, none of those children had an excessive dose. So that there did not appear to be any misinterpretation of the dosing instructions that

might have contributed to those occurrences.

The specific instructions on how to dose the medication: There was a w eight-specific label on the product, and the instructi ons that we provided to our enrolling practitioners was to identify the dose category that the parents should use, using th e product.

We didn't sit in those 1700 practitioners ' officers. So I don't know how that was actually done for 84,000 children. I, unfortunately, can't answer the question of how much time was spent to educate th e parents about what specific dose to use.

DR. PUCINO: So the clinicians basically dosed the product?

DR. LESKO: The clinician provided th e education. The dosing instructions were on the label , but the physician was instructed to dose based o n weight, and then how that was actually conveyed to th e parent was at the discretion of the physician.

DR. PUCINO: And just one othe r question. In terms of any type of liver toxicity, elevation , transaminations, was that even assessed?

DR. LESKO: By looking at hospita l discharge diagnoses for the entire 84,000 children , there were no cases of liver failure or hepati c

necrosis identified. There was only one child with a diagnosis of hepatitis, and that child had a concurrent diagnosis of mononucleosis, which may well have been the contributing factor.

DR. SOLLER: Dr. Pucino, if I could just make a comment, just reflecting on how we were using the different databases that we're presenting to you today. We included the Lesko, et al. information in terms of considering lower age limit and the basic safety, and then separated that from a separate study, two studies, the surveys, in terms of looking at the teaspoon amounts for the dropper product.

So they are just not to confuse one, trying to show the other. So they're separated.

CHAIRMAN D'AGOSTINO: Daniel, you had a comment? Evidently, you don't have it anymore. Mary Anne?

DR. KODA-KIMBLE: Yes. My question is for Dr. Temple. Were you -- Can you tell me, do you know how many queries you had about use of adult products for children?

DR. TEMPLE: I'm not sure how those have been coded. I have somebody here who's an expert. Do you have any way to know that number? We can look at that.

We were looking at -- These were inquiries about the use of these drops and liquids. We do get inquiries about -- I know we get inquiries about the use of adult products in children. I don't know how to compare those numbers.

DR. KODA-KIMBLE: The reason I'm asking is I'm impressed by most of the -- I think a lot of the major events are use of adult products in kids, inappropriate use of adult products in kids.

I'm also concerned about adolescents, and I know it's very dangerous to be thinking about any one case, but I'm still -- In my mind, I'm hearing this case of the 11-year-old 31kg kid who was given extra strength Tylenol, and you see the weight ranges in adolescents.

I'm wondering how -- and I wasn't on the committee before. So I don't know the history of how we got the breakdown at age 12 you can start using adult doses, and I'm impressed by the kinetic data that correlates appropriate dose with weight.

So, you know, can you give me a little history on that?

DR. TEMPLE: I can't do that history very well, but let me make a couple of comments. The labeling for adult products like extra strength

acetaminophen says not for use in children under age 12. So it's on the label right now.

Unfortunately, people don't follow that instruction sometimes. Secondly, the 12-year-old level was picked many, many, many years ago. I think Debbie tried to describe that, but I just forgot the year you talked about that, but it's clearly been maybe a couple of decades or more as the cutoff between adult products and children.

It is an argument for weight based dosing as a way to approach this, to a certain degree.

DR. KODA-KIMBLE: My other question -- I don't know whether you have any insight on this -- is to what extent are pediatricians specifically educated regarding these two products, the droppers and the -- Do they know? How familiar are they with the different concentration in these products and to warn parents about carefully selecting the products?

DR. TEMPLE: Well, most manufacturers provide education materials, and we pass out tens of millions of pieces of information every year, but clearly, in some of these cases, they weren't specific enough. They would say a teaspoonful of the brand name and not specify the form.

So we think we could continue to educate

health practitioners to do an even better job of communicating this properly.

DR. SOLLER: Dr. Koda-Kimble, we've had discussions on our task group relative to the health professional education component of this, and had not, in terms of putting all this together, come to grips to how that would be done; but I think what Tony is saying in terms of -- is reflective of McNeil practice.

Other companies, particularly the brand name companies, are providing a lot of information. As we might put more information on the label in a better form, that also would get out into the mainstream.

CHAIRMAN D'AGOSTINO: Ralph, you have some experience. Do you want to just comment on that, as a somewhat practicing pediatrician?

DR. KAUFFMAN: Somewhat practicing, yeah. I don't have any specific information for you. Again, it's anecdotal.

I think physicians have that information, and in the back of their mind they're aware of it, but at the moment they are answering the phone or returning the call, they don't think about it consciously. So my guess is that most of the time

these errors on the part of giving advice, of not being specific, is a matter of omitting information they know, but they just don't think to convey it at that moment in time.

DR. SOLLER: Certainly, if we had the information on the label and that telephone call is being made, and the physician says be sure you read the label for dosage, it might reinforce that.

CHAIRMAN D'AGOSTINO: Eric?

DR. BRASS: As we consider the safety profile of these compounds in children under the age of two, one is struck by the relative paucity and small numbers involved in the studies, and even in Dr. Lesko's very well conducted study the actual numbers are relatively small.

Therefore, the context of what we know about the agents becomes more important. Again, I'm not a pediatrician, but my recollection is that, when infants under two get sick, the risk of dehydration is greater than in a six-year-old. Therefore, a drug like ibuprofen, which may be more likely to cause renal failure in a dehydrated person, that when I look at the incidents of creatinines over 0.7 in a hospitalized patient, I see zero percent versus 6 percent; and while that may not be statistically

significant in the context of what we know about the populations and the drugs, it, nonetheless, causes me concern whether or not ibuprofen is as safe as acetaminophen for vomiting children under the age of two.

Can anybody comment on how I might be able to resolve that kind of question?

DR. SOLLER: I think we had some discussions within our group on that, and Dr. Snodgrass and Dr. Kauffman -- I think you have some comments, Dr. Weisman, and I --

DR. TEMPLE: Yes. Let me just preface this. When we did the switch of Children's Motrin in '95, this issue was discussed., and the product was switched.

DR. BRASS: I remember. Yes, but -- Again, but the two-year-old, now focusing on the under-two for today's discussion --

DR. SOLLER: Well, this gets into where you make that break, two, four, six months, and that's what I was referring to in terms of our discussions, and maybe we can take individual thoughts from practice.

DR. SNODGRASS: Maybe I can ask the question a different way. Are you asking should one

product -- have the age limit lowered and the other not?

DR. BRASS: That is a reasonable question from the kind of context I have drawn. Yes.

DR. SNODGRASS: Yes. Well, I think the -- and I've written a commentary on the pediatric therapy newsletters three or four years ago, addressing this possible issue. So I think the suggestion is there.

The absolute rate may be fairly low, but I think it's an area for education of professionals about this, but I think the absolute rate is low. I was actually -- Personally, I was quite surprised by the Boston fever study results. It looked incredibly benign. So I didn't predict that outcome, thinking along the lines you were suggesting.

So I think the rate is relatively so low, and if you take a one in 100,000 risk rate or one in 1 million risk rate, one in 1 million -- divide your 70-year lifespan into one in 1 million parts. That's a half-hour of your life.

So you got to put these kinds of things in that perspective, at what risk rate are we. I think it's so low that, although what you're suggesting is correct and there needs to be more study, but in fact as an issue as to whether you would lower it to two

months or not, I don't think that would have impact in a relative risk sense.

DR. WEISMAN: I think that, if you look at all of the studies that have looked at children either down to the six-month marker or the two-month marker, again that incidence is incredibly low; and if you were to add into that one other group of children that are admitted to the hospital with fever that have not taken either of the analgesics, the incidence of dehydration and renal failure among that group is probably higher than we're seeing in either of the analgesic treatment groups.

So that I don't think it's of any great significance, and I don't think that there is really any evidence to suggest that either drug would increase the risk.

CHAIRMAN D'AGOSTINO: Patricia had a question. Then Daniel. Then Lynn and Frank.

DR. SOLLER: I think Dr. Kauffman had a remark that he wanted to make.

CHAIRMAN D'AGOSTINO: I'm sorry. Please do. I thought you were finished.

DR. KAUFFMAN: Just very briefly, I was going to say we dealt with this a great deal on the Boston fever study. I happened to chair the Oversight

Committee for that study, and we worried a lot about the renal effects. Particularly, the nephrology people on the Oversight group worried about that a lot.

We were also surprised as these data unfolded, as we met regularly to look without breaking the blind but looking at the two groups blinded, to see if there was a discrepancy in outcomes; and we were, frankly, surprised.

The renal effect in this age group so far has turned out to be a theoretical worry. There really aren't data in any of the work that's been done in testing them in fever to substantiate that worry. It's been an issue in the older adult population primarily.

CHAIRMAN D'AGOSTINO: Patricia.

DR. SOLLER: In the archives of internal medicine in the early eighties, there's a case series of about 20 patients, therapeutic dosing, ibuprofen, all in renal failure. I think about three of those are -- Certainly, three of the childhood age group may be under age six.

Generally speaking, young patients tend to recover renal function compared to the elderly.

DR. KAUFFMAN: But there are, as you

probably know, a handful of case reports in the literature over the last eight years of young children who took one of the NSAIDs in a low volume state and developed reversible renal failure.

CHAIRMAN D'AGOSTINO: Thank you. Patricia.

DR. McGRATH: I wonder if, in the material provided to physicians as the educational material, if there are guidelines provided about dosing by weight for children under two in terms of current products, and whether it's proposed to provide consistent information in the section where it says "consult a physician" if the minimum age is changed to six months or two months or whatever?

DR. TEMPLE: All our educational materials to physicians do already give doses, recommended doses, for them to consider under age two, go down to four months or lower. So they are in there. I even think the Canadian drops already have it on their label. Is that right? Acetaminophen? Yes.

CHAIRMAN D'AGOSTINO: Daniel, do you have a comment?

DR. LOVELL: Yes, several comments.

There was an article provided to us in our review materials by Simon that was pretty sobering,

and that was the fact that in an emergency room setting, when they provide to the parents the product label and their selection of dosing devices and the weight of the child that was measured in the emergency room that evening, only 30 percent of the patients got it right in terms of actually measuring out the dose for their own child.

So that it's -- I think we still need to address the fact that there's a large gap here between what we might write down on the label and actually getting the right dose in the child, and I'd like the group to address that.

At the same time, I think it's related -- Some comments were made about how to improve the actual user friendliness of the dosing cup in terms of more clearly delineating the marks on the dosing cup. As a physician and a parent, I can tell you that is an issue, especially in the middle of the night, because it's not clearly delineated.

There was also a comment made about why we get hung up or whatever, continue to use teaspoons on our device, when in fact it might encourage parents to throw your dosing cup out and use the teaspoon or at least passively maybe supports that transfer.

DR. SOLLER: Just a comment on the Simon

study. We were, frankly, stumped by what to do with that information, and I'll tell you why in a moment. I don't want to reflect -- have my comments reflect the fact that we don't appreciate the need to communicate well and for people to access the information and use it well. That's very important.

We were very surprised by the finding that the -- Well, before you nod your head, let me tell you the finding that we were surprised by. That is that they were told the weight of the child, and then in an emergency room setting -- and there are a lot of things going on in that setting -- they weren't able to accurately do the dosing.

What I don't know from the study is whether they were really asked to do this on or about the time the child is in the room, before that, or after that when they have a relief and they're not worried about anything.

So I think you have a different situation there, and I don't think that that study transfers over into a home setting. I think that's sort of the anomaly of that study.

Now insofar as the cup --

DR. TEMPLE: Yes. Well, let me make one more comment about it. I talked to Dr. Simon about

his study, and he's very amiable about it. He says that there are some concerns, obviously, raised, but the bigger issue, he said, was this wasn't an in-home situation. A lot of people didn't even ask for the labeling when we asked them the questions.

So it was not a labeling comprehension test at all or ability to understand it. So there are a whole host of issues. It was again people trying to remember what had happened, and there was a lot of parent guessing. Even though they had it available to them, they didn't use it.

That raises a whole set of other issues about it. We do need to encourage parents to read the label every time they take the product. We've just got to say that time and time and time again. So anything you can do to help us with that, we'd love to do. That's number one.

Now the dosing cup: There have been recommendations to try to enhance the markers. I've heard that a couple of times. It is just a question of the technology of getting that done.

The question about teaspoons versus milliliters: I think the industry practice has been to use teaspoons, because that is the most familiar still to the parent who uses these kinds of volumes.

Somehow, as much as we've tried to create metric thinking, it hasn't got much beyond the healt h professional community, and there not so well.

So we just haven't got it into the homes yet. So we're using common terms. We need to work a t that, I think, to help people understand th e comparisons, though.

On the label we're saying one teaspoon equals 5ml. Maybe someday we can make the transition .

DR. LOVELL: Well, though, I'm not sur e that it's necessary to put any volumetric measure on your dosing cup. Why don't you just put age of th e child, if that's -- so you can -- the breakdowns are there, rather than volumes.

DR. SOLLER: I think that it's possibl e that we have a cup with a lot of information on i t now, that if you look at the teaspoon demarcations an d then thought about, well, do we put weights on there as well, because we have both of those schedules? So that could represent an overabundance of information on the dosing cup.

So I think we're trying to keep it simple , and I think what we're trying to convey are concepts to work on how that might be done.

DR. LOVELL: But I still think the point

needs to be addressed as to how to make this more easily -- or the cup could be more discretely marked so that it's easier to see when you have opaque solutions in the cup.

The other thing that came up: In your instructions here, direction number 5 says no more than five times a day. Was there a discussion as to whether to use day versus 24 hours, because, really, accurately what you're talking about is five times in 24 hours. Correct?

DR. SOLLER; Yes. In fact, what I did for that particular part of it was to simply take it off, I think, this label. We did not specifically address that within that portion of the presentation, trying to convey the hourly and the daily rate. You may have some --

DR. TEMPLE: That's just the current FDA language that we've been using for a long, long time, using day rather than 24 hours. It's just current standard terminology. You're input, I'm sure they're listening to.

CHAIRMAN D'AGOSTINO: Lynn?

DR. McKINLEY-GRANT: I had a question about the cold remedies that contain acetaminophen. is there -- In terms of the inquiries that you get,

Dr. Temple, is there -- Do you get a lot of inquiries about the use of the two medications or I'm even wondering with poison control if people suddenly realize, oh, I used both medications. I gave the child Tylenol, and I gave him something with acetaminophen in it, because those bottles tend -- The cold remedies tend not to be clearly marked that they contain -- They will say fever reduction, but they may not boldly state that acetaminophen is present.

DR. TEMPLE: Unfortunately, I can only talk about our experience with our own brands. We will get questions about whether you can use two drugs at the same time, and of course, we tell them no. They're labeled. It says "do not use with other acetaminophen containing products." We hope that communicates effectively.

We hope that the fact that it's a common brand name maybe communicates effectively, but we don't -- I know from what Dr. Litovitz has said that there are some exposures where concomitantly both products are used, yes.

CHAIRMAN D'AGOSTINO: Frank?

DR. PUCINO: Yes. A question for Dr. Soller. Realizing these two studies are different and the intent was different, in a controlled environment

such as the fever study there were very similar adverse effects between the two products, but looking through the graphics on the NDMA study, it almost appears that the nonsteroidal group had about a four or five times greater incidence of more serious adverse effects. Could you comment on that?

DR. SOLLER: You're looking at Tab --

DR. PUCINO: Tab 3.

DR. SOLLER: -- Tab 3, page --

DR. PUCINO: Eight.

DR. SOLLER: I'm sorry. I'm now on the same page with you. Could you repeat your question?

DR. PUCINO: The question is: Realizing the two studies are different and the intent is different, in a controlled environment the two products appear very similar in terms of adverse effects, in terms of their profiles; but according to this graphic, as best I can understand it, it almost appears that the ibuprofen group had about a four or five times greater incidence of serious adverse effects.

DR. TEMPLE; It's a new introduction, and the experience is that during these two years you're going to get a lot more reports with a new introduction than you'll get subsequently. I think we

have seen that pattern.

We get a very sharp rise of calls to our company, and then we'll taper off after that. So these rates are not really comparable in terms of overall rates. You can't make that comparison.

CHAIRMAN D'AGOSTINO: Other comments or questions from the consultants, from the FDA?

It's a little after twelve. Why don't we come back at one. Is there anyone at the table who has to leave, say, before three o'clock? So we should be in good time. Let's come back at one o'clock, please.

(Whereupon, the foregoing matter went off the record at 12:02 p.m.)

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

(1:04 p.m.)

CHAIRMAN D'AGOSTINO: We are now going into the open public hearing, and there's one presentation and one letter which is going to be read. Why don't we start off with the presentation, Dr. Philip Walson.

Would you please identify yourself and your affiliation, and if anyone is supporting you to come here.

DR. WALSON: My name is Philip Walson. I am Chief of Clinical Pharmacology and Toxicology at Children's Hospital in Columbus and Professor of Pediatrics Pharmacology and Pharmacy at the Ohio State University, and today basically I'm representing -- I'm on behalf of Whitehall-Robins, but I should reveal that I have lots of other hats.

I've been a consultant to many pharmaceutical companies that manufacture analgesics/antipyretics. I am Chair of the USP Pediatric Panel. I was just made a member of the American Academy of Pediatrics Committee on Drugs. I run one of the AAPCC poison centers that's regionally certified that provided some data.

I've conducted 14 clinical trials of

ibuprofen and acetaminophen as analgesics and antipyretic agents in children, some published, some soon to be published, some perhaps never published.

In these -- They've enrolled hundreds of children. Three of them included children under -- at least as young as six months. I also am a practicing pediatrician and have an active hospital based practice as both a pediatric clinical pharmacologist and as a toxicologist treating patients with therapeutic and other misadventures associated with these drugs.

I'm also the PI of one of the seven NICHD funded pediatric pharmacology research units around the country, and we are involved in at least three trials as a network of antipyretic agents.

Let me go through a few things. One is that I want to clarify an issue about creatinines, since there is a published paper by Kelly et al. My name is on it, where we took over 200 children that were given ibuprofen in various studies that we had done to date. I think that's about five years.

In fact, creatinine in the treated group went down compared to both acetaminophen and placebo treated children, not up, an interesting finding, but in fact true.

I'm here to support the lowering of the age limit for OTC analgesics and antipyretics down to at least six months, and there's lots of reasons. One is there's adequate data existing to document the antipyretic effectiveness of these drugs in this age group, and at least inferential data that indicates that they are effective analgesics.

Dosing instructions on the label of OTC products could provide parents and caretakers with a readily available reference to help remind them of the proper dose to administer. Without these important data on the label, dosing instructions would be neither standardized nor controlled.

This would, in fact, increase rather than decrease the risk of any adverse effect of these drugs, including inadvertently administering an inappropriate dose.

Another thing I would like to support is the elimination of dosing based on temperature. This is neither scientifically nor statistically justified and makes no sense. As a clinician, I also think -- and I have seen this create unnecessary complexity.

It also incorrectly implies to parents that the magnitude of a temperature indicates the seriousness of the underlying illness. It also

creates confusion and is illogical, because temperature can vary depending upon the site of measurement, the instrument being used, the skill and method of the temperature taker.

There is no evidence that shows the parents can reliably measure a temperature, and certainly no evidence that 102.4 should be dosed differently than 102.5, which current labeling suggests.

For that reason, I think for OTC ibuprofen a single uniform approximately 7.5mg per kilogram dose is preferable. this is the approved OTC dose in children age two years of age and older. This dose is both clearly effective and should be well tolerated, as the data clearly show, by the vast majority of children.

The data presented already by Doctors Soller, Lesko, Temple, and Litovitz clearly demonstrate the safety of this product in actual experience in this population.

I also think it's desirable for ibuprofen to be available in both suspension and drops. Very young children may be unwilling or developmentally unable to take medications via spoon or dosing cup. Maybe the correct political term is they are

developmentally challenged.

A concentrated dropper formulation provides a convenient and often essential alternative to effectively administer antipyretics to children uncomfortable from pain or fever. I might add that these drops are very useful in children up to the age of eighties, that sometimes they are very useful in all age children.

In conclusion, I want to echo the recommendations of previous speakers to lower the age limit for OTC antipyretics to at least six months, and to have a single average, approximately 7.5mg per kilogram ibuprofen dose indicated for children.

I also endorse the continuing availability of both drops and suspension. These products, both ibuprofen and acetaminophen, are already in widespread use in children under two. This will not change, based on what you do or not do on the label, but providing labeled information on both products will increase the safety of this ongoing and increasing use.

Thank you. Any questions?

CHAIRMAN D'AGOSTINO: Thank you. Andrea is now going to read a letter.

DR. NEAL: This is a letter that was

submitted by a parent that I've been asked to read. It comes from Michael Murphy of Glendora, California.

"Dear Committee Members, Thank you for taking the time to listen to and consider my comments. I believe the work you are doing is vitally important to the wellbeing of our country, and especially valuable to those of us who are administering over-the-counter drugs to small children.

"On Saturday, March 22, 1997, my two-year-old son died form anaphylaxis brought on by an allergic reaction to Children's Motrin. (A complete report has been submitted to the FDA, should you wish to examine the details of this event.)

"We administered this drug following the package direction carefully. When my son woke up from his nap with a puffy face, we immediately suspected he was having an allergic reaction to the Motrin and called his doctor. Unfortunately, we were given tragically bad advice by my son's doctor, who simply told us to stop giving Billy Motrin and continue treating his stomach virus as we had been, by keeping him on a liquid diet of Pedialyte.

"Both my wife and I were by Billy's side when he stopped breathing. I immediately began mouth-to-mouth, as my wife called 911. Within minutes the

police arrived, and Billy was rushed to the hospital in the back of the squad car with a paramedic performing CPR.

"My son never responded to treatment in the emergency room, and was pronounced dead about 45 minutes after arriving.

"In addition to the bad advice I received from my son's doctor, I was hampered in two other ways. First of all, Billy's worsening condition was masked by the symptoms of his stomach virus.

"I learned in my study since his death that vomiting and flu-like symptoms can be a warning sign of anaphylaxis. Billy had these symptoms already, and there would be no way to differentiate from his stomach and an adverse drug reaction.

"Our doctor should have known this and warned us of the more subtle changes we needed to look out for, such as shallow breathing and irregular heartbeat. We were not checking our son's heartbeat. In our minds, all we were treating was a stomach virus.

"There was no reason to check his heart, and Billy's breathing must have been labored, but he was not yet speaking more than one-word sentences and, therefore, unable to tell us he was having trouble.

"He was not wheezing or gasping for air. So we had no outward sign that he was getting worse. He looked weak and tired, just as his sister had on her last day with the same virus a few days earlier.

"Simply put, special precautions need to be taken when giving drugs to infant children who are unable to articulate when they are having difficulty.

"Finally, I was also hampered by the inadequately labeled Children's Motrin box. After my son's death, I was shocked when I found the following warning in the 1995 edition of The Complete Drug Reference: 'Nonsteroidal anti-inflammatory drugs may cause a serious type of allergic reaction called anaphylaxis...Signs may include...puffiness or swelling of the eyelids or around the eyes. If these events occur, get emergency help at once.'

"This is precisely the reaction my son was having, but no such warning appears anywhere on the Children's Motrin box. I was stunned even more when I found the following in The Physician's Desk Reference, referring to aspirin sensitive children: 'Severe anaphylactic-like reactions to ibuprofen have been reported in such patients, some with fatal outcome.'

"The Children's Motrin box does have a

warning regarding aspirin sensitive children, but most parents in America do not give their children aspirin, and for that reason, most parents in America do not know if their children are aspirin sensitive. Therefore, this warning is almost useless.

"In addition, this warning does not mention the need for immediate emergency medical care, should your child exhibit such a reaction.

"Children's Motrin has a potentially fatal side effect, and appropriate precautions should be clearly outlined on the box. There is no question in my mind that the warning from The Complete Drug Reference should be on the Children's Motrin box or something close to it, such as the following:

"Possible allergic reaction: This product may cause a rare, severe allergic reaction. Signs may include changes in color of the skin of the face, very fast but irregular heartbeat or pulse, hive-like swellings on the skin, and puffiness or swelling of the eyelids or around the eyes. IF THESE EFFECTS OCCUR, GET EMERGENCY HELP AT ONCE.

"I know, if this warning had been on the Children's Motrin box, I would have ignored my incompetent doctor and rushed my son to the emergency room, and he would still be alive today.

"I understand that there are many drugs that can potentially cause this anaphylactic reaction, and perhaps there needs to be a standard anaphylaxis warning outlining symptoms to look for, and focusing on the needs for immediate emergency medical treatment.

"Children's Motrin, as well as other over-the-counter medications, need to be labeled in such a way that even those who don't have the benefit of a regular doctor to call for advice can administer these drugs, knowing full well the risk involved and the precautions needed.

"Drug companies do not want to put warnings on their products that might frighten customers away. My deepest concern is that their desire for maximum profits might cloud their judgment in regards to appropriate warnings.

"It is my hope that the FDA will more closely monitor the negative side effects of over-the-counter drugs and demand that drug companies label their products appropriately."

CHAIRMAN D'AGOSTINO: Thank you, Andrea.

I've been asked by the Nonprescription Drug Manufacturers Association to call attention that some of the presenters or some of their consultants

will be leaving shortly, possibly leaving shortly; and if there's any questions from the panel, they would like to be able to address them now.

Are there any outstanding questions that we need to get back to them about? Yes, Mary Anne?

DR. KODA-KIMBLE: Well, I had a question for Dr. Berlin, but since others may be leaving: Dr. Berlin alluded to the fact, and I'm trying to recall, that febrile children may be more susceptible, less susceptible to the toxic effect of Tylenol.

Was there a statement like that, and does anybody know anything about the effect of fever on the kinetics or toxicity of acetaminophen?

DR. KAUFFMAN: I'm Ralph Kauffman from Children's Mercy Hospital in Kansas City. I'll try to answer your question. Before I do, I need to state that I am here as a consultant today for McNeil Consumer Products.

Chet and I have worked on the Committee on Drugs for a number of years together, and Chet just rotated off as Chair of that committee subsequent to the four years that I chaired it.

With respect to the susceptibility to -- illness causing susceptibility to adverse effects of either drug, I think there are very few data

specifically addressing that. What I thought I heard Chet saying was that illness, at least theoretically, may alter the response to these medications.

I don't think -- and correct me if you know differently. I don't think there's good information that says that common childhood febrile illnesses alter the pharmacokinetics of acetaminophen or ibuprofen.

Certainly, salicylates they do, because salicylate at fairly low concentrations undergoes saturation kinetics, and so one starts seeing zero order kinetics, and particularly with dehydration where the elimination becomes very dependent on renal output, but aspirin really isn't a major consideration here today.

That does not occur with the other two compounds. As was brought up earlier, dehydration could predispose a child to a low volume state where renal blood flow becomes increasingly dependent on prostaglandin synthesis at the renal -- at the efferent vessel.

So that renal blood flow can at least be transiently reduced if a nonsteroidal or a cyclo-oxygenase inhibitor is administered under those circumstances. That's very volume dependent.

It's a theoretical consideration at least. There is very little information that says it's a significant risk factor, but it's something that I think we need to always keep in the back of our minds.

With respect to acetaminophen, there also has been -- Wayne may want to comment on this. There has been - There's at least some animal data looking at glutathione turnover in the liver with short term starvation states that have to do with gastroenteritis or an acute febrile illness where the child is not eating, and nutrient intake is decreased, but it isn't clear that that really alters the usual doses of acetaminophen that are ingested.

Do you know anything more about that, Wayne?

DR. SNODGRASS: I'm Wayne Snodgrass. I'm also here through McNeil Labs.

We did some work several years ago that looked at the acetaminophen cysteine and mercuric acid conjugate. The ends are small, three, four, five children per group, but afebrile versus febrile, and there was no difference in the percent excretion of those toxic -- mean quinone mean marker pathway.

So that that would suggest that there is no major effect in well nutritioned children, if you

will, of that. What Dr. Kauffman is referring to about the glutathione is, of course, lower liver content of GSH in significantly malnourished Kwashiorkor, for example, infants or the equivalent animal model.

So I think I'm not aware of specific data as to what Dr. Berlin was referring to, but a potential concern.

CHAIRMAN D'AGOSTINO: Thank you. What I'd like to do now is turn to --

DR. McKINLEY-GRANT: Ralph?

CHAIRMAN D'AGOSTINO: I'm sorry.

DR. McKINLEY-GRANT: One question. That is: What is the -- We're using two drugs sort of interchangeably, acetaminophen and ibuprofen. What's the actual use by pediatricians of ibuprofen in ages below two? Is it widely used or as widely used as acetaminophen is?

DR. TEMPLE: Dr. Temple again. They're both widely used. It's about 60 percent acetaminophen, about 40 percent ibuprofen, approximately, at this point.

DR. McKINLEY-GRANT: And for -- the ibuprofen for a fever or pain?

DR. TEMPLE: It probably is a slightly

higher proportion of use for pain with ibuprofen, slightly less than for fever, not big differences, though.

CHAIRMAN D'AGOSTINO: Are there other questions? No? Then Dr. Katz will give the charge to the committee.

DR. KATZ: Good afternoon.

What I'd like to do briefly is to summarize where we've been earlier today before giving the charge to the committee to deliberate on the questions that they have at hand in their package.

We've heard discussion this morning regarding the history of the OTC dosing of these analgesic-antipyretic children's products, the pharmacokinetic make-up and how pharmacokinetics may influence or impact on dosing, the adverse event profiles that we've had on these products that are contained within the SRS database, as well as some overdose information that we have from the test database, and opinions from the pediatric community as well as industry regarding these products and the issues at hand.

It's important to remember that OTC medication errors may occur as a result of several different factors. One may be a prescribing error in

that inappropriate dose selection may occur, dose or dosage form, quantity, route of administrations of misunderstanding of instructions for use.

Medication errors may also occur as a result of incorrect dose error in which a patient receives too little so that they don't get the desired therapeutic effect, or too much. That results in an overdose, and (3) the wrong dosage form may be selected, either a selection of a drop for a suspension when one was wanting to use the suspension product or selecting an adult product in place of a children's product or even selection of suppository product, an adult product versus a child's product, because of some confusion about either age or dosing routes themselves.

The concerns addressed about these products really focused predominantly on the mistakes made by caregivers, and that these mistakes really are unintentional mistakes that we're trying to focus on, that the mistakes may have resulted from health practitioners giving misinformation to parents and their inability to be able to check this information, because labeling may not have occurred to corroborate or to go back and check to make sure that the dosing instructions that they were being given were

consistent with the product that was being used because the product fails to label below two years of age.

Other unintentional mistakes may occur as a result of failure to read the label thoroughly or failure to understand the labeled instructions, failure to inform the practitioner of the actual product that one has at home, so that when the practitioner gave the advice, as we've heard, that they give a dose for a product that they assume that the parent may have had or the caregiver may have had, when in fact they had a different product available to them, or the inappropriate use of a dosing instrument, which we've also addressed.

It is also important to remember that the currently available OTC analgesic/antipyretic products that are out there on the market now are labeled for children greater than or equal to two years of age. There is also an additional concern that we need to focus on this afternoon as well, which is an overlapping age, that some products are labeled predominantly for two-to-three -years which are double concentrated drops, and yet for the suspension or we have the -- starting at age two to three, which also creates some problems or confusion from the consumers.

Again, even though we've not spent a great deal of time talking about this issue, we also need to be concerned about the suppository products that do exist on the market for children in this age group, and also confusion that may result because of the labeling instructions.

This meeting -- In this meeting we have chosen to very narrowly focus our charge to you on the single ingredient analgesic/antipyretic products. The reason for that really goes back to some of the history and, in fact, dates back probably two years ago when this issue was addressed at the Advisory Committee then.

We saw from slides earlier from presenters that the issue was addressed, well, how low do we go. The advice given back to the agency, well, it's a case by case approach. So here we are with a specific case, single ingredient analgesic/antipyretic product, and we're now asking for advice.

We do realize that there are combination products out there that do contain analgesics, and we do realize that there is potential for overdosing because a parent may not be able to understand that they're giving a cough/cold preparation that has an analgesic, plus they're giving an analgesic product;

but we don't want to address that in this meeting specifically.

Hopefully, when the OTC labeling formats become finalized and when parents and consumers and whoever else is using a product can see the active ingredient higher up on the panels that they will realize what the active ingredients are, some of that may be taken care of. If not, obviously, we can discuss it again at some point in time.

We also do realize that there are other products that are available on the market that are being given incorrectly, and again I mention adult products to children. We're not focusing on that issue now. We are predominantly focusing on the children's products.

So that with these caveats in mind, I would like to have you focus your attention on the questions provided in the background material and in the agenda that were available outside the room when you came in earlier today.

These questions are: Given thee safety implications discussed for the OTC analgesic/antipyretic suspension and double concentrated drops: (1) should labeling for overlapping agents be permitted? Again, I'm referring

to the two-to-three-year age group that we've talked about.

(b) What labeling modifications do you suggest to prevent unintentional overdose.

2. Can single ingredient analgesic/antipyretic suspension products be safely and effectively labeled for use in children less than two years of age? If so, what is an appropriate lower age limit?

3. What, if any, other labeling recommendations do you have?

At this time, I'll turn back over the meeting to our Chair, and thank you very much.

CHAIRMAN D'AGOSTINO: Thank you. Are there any questions for Dr. Katz at this moment? There will be, I'm sure, as we go through the questions before the committee and, hopefully, at that point clarification can be produced, as needed.

Some of these questions are written in such a way that votes could be taken. I think what we'll do is we'll just go through the questions and see if they're appropriate for votes as we go through them.

There are voting members and nonvoting members around the table and, if you would please

check the status when we do come to votes, and we'll also check; but just to clarify that issue.

Now the very first question be fore us is:

Given the safety implications discusse d for the OTC suspension and dou ble concentrated drops, should labeling be permitted for overlapping ages?

Now I'd like clarification on what th e concern is. We understand from the material presente d that there are potential adverse effects when th e drops are given incorrectly. So there is a concer n that one has to do that appropriately.

The overlapping ages is that the drops sa y two to three years on the label, and the liquids say two to 11. Is that correct? Is that how it goes?

What is the concern in keeping it the way it is? I mean, what would be the alternative, say th e drops 2 to 11?

DR. KATZ; Well, one of the issues that w e bring up is should the drops be labeled for a finite age group, and should the susp ension be labeled for a finite age group, so that a consumer who has a child of two years of age would have one specific product, and a practitioner would get used to that tha t individual would have that par ticular product, rather than in the middle of the night a consumer buying a

product for, let's say, a two- year-old but not really intending to use it for a two- year-old, and it may -- there may be some way to try to differentiate.

If one decides to go lower for these products, which products would be more appropriate for a lower age group, which products might be more appropriate for a higher age group, and that's where the question comes from.

CHAIRMAN D'AGOSTINO: Are there any comments? Michael, did you want to make comments?

DR. WEINTRAUB: No, that's the question that we're really interested in.

CHAIRMAN D'AGOSTINO: Why don't we open it for -- Do you have a comment?

DR. KAUFFMAN: Yes, if I may. I think that any age distinction that is made to divide the two dosage formulations is going to be artificial, because in the real world there's an enormous amount of overlap.

The development of a child is a continuum. It's not an abrupt sequence. So there will be two-year-olds who might take from a cup. There will be an occasional two-year-old who wouldn't, if you decided that two years was a break point.

You might decide three years is a break

point or younger than two years, but I think there's merit in maintaining the flexibility for a parent to use either of two formulations, depending on what their child's developmental level is in that overlap age period; because kids vary tremendously developmentally and ability-wise.

I've tried to struggle in my own mind how would we do a single preparation that would serve the entire age spectrum to deal with the issue that Dr. Berlin brought up this morning. The problem is, if we try to use a single concentration, either a more concentrated preparation like the drops or a less concentrated one like the elixirs or solutions, we're going to be subjecting the extreme -- the groups at the extreme age range, ends of the age spectrum, to probably increased errors, because if we use a less dilute or a more -- I'm sorry, a more dilute preparation down in the infants, we're going to run into problems in measuring it in a -- with a device that the infants could use readily.

If we use the more concentrated formulation in the older kids, we're going to run in at the lower end of the age range of the older kids, in the three, four, five year age group, the volume administered would be low enough that we would

increase the risk of dosing errors, simply because of accuracy in measuring the volume in the home situation, and the palatability is -- It's a secondary issue, but it's an issue, too.

So I -- In my own mind, I haven't been able to figure out how we would do this, if we -- even if the decision was made, and reduce the risk to this entire childhood population from six months up to 12 years.

For practical administration and trying to give the parent the best flexibility and the best option to dose as accurately as can be done in the home setting using either weight or age, I think we really need two types of formulations, and maintain that flexibility.

CHAIRMAN D'AGOSTINO: Thank you. I'd like to open the discussion to the members around the table. Any comments on this?

DR. McKINLEY-GRANT: Two comments: One is I wonder if -- In terms of our discussion we're saying analgesic/antipyretic. Now we're specifically referring to acetaminophen and ibuprofen. Is that right? We're not including aspirin or --

CHAIRMAN D'AGOSTINO: Well, the dose, the drops and the liquids -- I mean --

DR. McKINLEY-GRANT: Yes. Well, just in terms of the term -- I mean we're talking about a spectrum of drugs, analgesics and antipyretics, as opposed to -- Usually, we're thinking in terms --

CHAIRMAN D'AGOSTINO: Well, this one here is -- This question is solely on suspensions.

DR. McKINLEY-GRANT: Right, but my concern is just, you know, when we look back on this 20 years from now, will someone say, oh, well, aspirin is included in this?

CHAIRMAN D'AGOSTINO: Well, it's not. The question is --

DR. McKINLEY-GRANT: No, just in terms of labeling and dosing of over-the-counter pediatric analgesic and antipyretics.

DR. KATZ: For this specific question, though, it's referring to the products that are currently available in those dosage forms. For some of the other questions, then, yes, it would broaden the spectrum.

DR. McKINLEY-GRANT: So aspirin is not available in a suspension?

DR. KATZ: That's correct.

DR. McKINLEY-GRANT: Okay. That's fine.

The other comment that I wanted to make - -

I do think that two forms are probably better. If you have an infant, you know, to try to get any form of anything in an infant, you lose half of it. So the drops tend to work very well, but I think the bottle should be -- and the packaging should be clearly distinguished, so that you have -- and by age even, if we could do it.

If we're starting with six months to two or three, and then three to 12, something like that, but I think you really need -- To safely administer the medicine, you really are going to need two different preparations.

CHAIRMAN D'AGOSTINO: I'm not clear on what your responses to this is. Are you saying there should be two separate age groups, non-overlapping age groups?

DR. McKINLEY-GRANT: I think there should be two separate age groups, and perhaps with the -- you know, to allow for the developmental things, the two-to-three-year-olds -- I have to leave it to the experts to decide on that, but I think if we're starting with six months to two, I wouldn't favor going one formula, or six months to 12 years old; but I would favor two formulas at six months to two, and then three to 12, something like that, with an overlap

in the two and three-year-old group.

CHAIRMAN D'AGOSTINO: So you are allowing an overlap, though?

DR. McKINLEY-GRANT: Right, with the drops, though, more so than with the suspension.

CHAIRMAN D'AGOSTINO: Well, I think the drops are two to three right now. If we can just stick to the ages two to three and worry about bringing it down to six months. The drops are two to three right now, and the liquid is two and above.

If I hear your response correctly, you're willing to basically live with that.

DR. McKINLEY-GRANT: Well, I think I would like the suspension -- because that seems to be the problem in terms of children getting a higher dose from the suspension. So I would like to see the suspension at three to 12.

CHAIRMAN D'AGOSTINO: So make it two to three for the drops and three to 11 or whatever for the suspension. Are there other comments? Eric.

DR. BRASS: I think the overlap intrinsically is not a problem. I think there may be problems related to label and comprehension, etcetera, etcetera, but I think the overlap intrinsically is not a problem.

I think the availability of different products for different consumers is good, and that consumers have proven that by buying different things under different circumstances.

Additionally, even the way -- Based on what we know, age isn't the optimal cutoff anyway. I s an underweight three-year-old and an overweight two-year-old, etcetera, etcetera -- So I think you have to provide a great deal of flexibility here, as long as the intent and use is unambiguous and the labeling facilitates the differentiation and minimizes the confusion.

CHAIRMAN D'AGOSTINO: The way the questions are laid out. So if you said that the labeling allow the overlapping ages, then you're saying go for the b) where you clarify what the label is.

DR. BRASS: That's right. So my answer to a) is yes.

CHAIRMAN D'AGOSTINO: Earl, do you have a comment on that?

DR. SILVERMAN: Well, Id' just like to agree with a). My only suggestion about the second part of how to overcome it: I think it was brought up when Lynn referred to the use of the word suspension.

As I look at the labeling, it says suspension drops and suspension liquid. That may be the confusion. One of the suggestions may be to eliminate the word right on the front of suspension drops and suspension liquid, so that there is no confusion at all possible. You may say infant drops, whatever, but one-half of it is the same word. That may lead to the confusion in the overlapping age groups.

CHAIRMAN D'AGOSTINO: Are there other comments? It probably is worth more discussion. Did you have a comment?

DR. LOVELL: Well, when you actually look at the data from overdoses from both the databases, the actual number of cases in which this turned out to be the source of overdose for the kids actually is a minority of the circumstances in which there was toxicity.

So it's turned out to be in the databases, I think, a much smaller problem than I would have predicted, thinking about it. So I think its not a major issue. I agree with Abe that the labeling is more of a problem. So I would vote in terms of allowing the overlapping ages.

CHAIRMAN D'AGOSTINO: Lynn, do you have

sympathy with the last few speakers in terms of --

DR. McKINLEY-GRANT: Oh, yes, I feel strongly, the labeling -- you know, there really need to be two separate bottles, you know, a little one for the drops and a bigger one for the -- and the labels look too much alike, in terms of even the pictures on the label. One has an infant. The other has a toddler. I mean, they really have to separate.

CHAIRMAN D'AGOSTINO: Let's -- Just so we can be specific, because we were asked to be specific by the FDA, let's take it to a vote, thinking that we have an a) and a b) part to hear.

We're looking at the a). We're saying should labeling be permitted for overlapping ages, keeping in mind, if we say yes for this, a number have expressed very strong concerns about size of package, labeling, and so forth, to clarify the two.

So let's take: Should labeling be permitted for the overlapping ages. All those in favor, please raise your hand. Any opposed? Any abstentions? For the record, how many was that? Eight-zero. Thank you.

What about the labeling modifications? Do we have any suggestions? We had stated some suggestions. They're obviously in the transcript, but

are there other suggestions or any reiteration of those? Eric?

DR. BRASS: This is a device technical question. Is it possible to build the dropper into the lid in a childproof way so that, when one had the drops, one couldn't miss it because the dropper was intrinsic to the packaging? That way, there wouldn't be any -- It would seem -- With having the dropper physically distinct, there's always the possibility of, again the middle of the night analogy, picking up the bottle without the dropper and not knowing which is which. Anybody?

CHAIRMAN D'AGOSTINO: Anybody have a response to that? Bill?

DR. SOLLER: Bill Soller, NDMA.

I am aware that there are some products that do have the dropper intrinsically, as you say, as part of a child resistant and dropper situation.

What I can't answer to you, and I don't know that this is necessarily an issue here, is that some of the CRP child resistant packaging is patented. So I don't know the extent to which this thing can be applied overall.

The P&G packaging on Naproxen, as an example, was one that has been used on different

products. So I can't -- I just don't know the reasons why that isn't used.

I will tell you that the dropper can be put back in. They're formulated with suitable stability kinds of requirements that allows that to happen.

CHAIRMAN D'AGOSTINO: Yes?

DR. ROGER BERLIN: I'm the other Dr. Berlin, Whitehall-Robins Health Care.

In terms of the proposal that you've just made, there are issues in terms of stability of the product when it's packaged in the --

CHAIRMAN D'AGOSTINO: Could you speak up? I'm sorry.

DR. ROGER BERLIN: Yes, I'm sorry. There are potential issues for the stability of the product when it is, in fact, packaged that way. Since these products -- It's very important to maintain their delivery of the drug, there would be at best a substantial delay before that could be implemented, if it's feasible, and I don't think we could necessarily guaranty that's feasible.

CHAIRMAN D'AGOSTINO: Thank you. Any other comments on that? If there aren't any further comments on 1, then why don't we move to the second

question. I'm sorry. I didn't see you.

DR. KATZ: I actually think there should be very strong attempts to differentiate between these different concentration products. I don't know how that might occur. Someone suggested that some of these have the term concentrated on them. Dose -- look at the dose carefully.

Any kind of signal to the parent who is on the -- you have to differentiate between these things on the shelf and in the middle of the night, that they've got to look at this thing twice in terms of the dosing.

I really like Eric's idea, though. Even if the thing were packaged separately, that it would be then screwed onto the cap so that it doesn't get separated and there's no other choice for dosing this thing except the dropper.

I think the most -- the one I'm most worried about is the more concentrated solution, but I agree, the data is not there to support that that's the biggest overdose issue.

CHAIRMAN D'AGOSTINO: Yes, Ted.

DR. TONG: I'd like to make a comment here. You know, we're concerned about overdose, and we clearly should be, because that ends up with

mortality and morbidity; but Dr. Lovell brought up the issue of the Simon studies out of Atlanta.

I thought the other interesting piece was that 50 percent of the caregivers gave -- underdosed the medication for treating the problem, and that sort of builds this sort of "if it's not working, let's give more."

In the other circumstance where with several children in the home, you really buy over-the-counter products just for the child, for one child, and there's also that switching. So in thinking about labeling and packaging, all those issues, that dynamic also has to be in place.

I'm glad you mentioned infant drops, baby drops. I don't think too many people that I encounter would understand what concentrate means, but even a simple statement like I just noticed on the packaging here -- suspension is mentioned in both, and that clearly would be confusing in someone just walking past the medicine cabinet and saying which is the right one to give to our child.

So I just want to make that comment to add to what everyone else was saying here about the labeling importance and the packaging and the teaching of our patients on how to use their over-the-counter

medicines.

CHAIRMAN D'AGOSTINO: I think it's correct to say that we do, by a vote, say the overlapping ages is all right, possibly not idea but certainly all right. It's in the labeling. We're not necessarily full of ideas on how best to handle that in the labeling, but we think it is a labeling issue. Is that correct?

Then can we move to 2? Now in 2 it's a question about with the suspension products again, moving the age from two to something under two years of age. The way it's written down, these products be safely and effectively labeled for direct use in children under two years of age.

We hear some presentations about the fact that the directions are not given for individuals under two years of age, and that may, in fact, be related to some of the misuses.

Tony gave a nice presentation this morning showing some graphs that did indicate the rise of misuse and so forth as you got younger, and was making suggestions about bringing it down to two months. am I quoting you correctly?

With the Boston fever study we have data that takes us down to six months, and I think maybe

the way to get into this, if you don't mind, Toby, if you would just give us a statement of where you feel we should be dealing with this question or how we should be dealing with it.

DR. LITOVITZ: Yes. You know, I think it's pretty clear that, with the products that are used in small children, and we know that at least at this point acetaminophen is regularly used, and ibuprofen is increasingly used -- that there are errors down to two months of age.

If you don't provide some guidance for the parent, I think the parent is going to end up continuing to make those errors. The competing argument, of course, is the drive to get the parent to call the pediatrician when a child has a fever, so that an evaluation can be made in the very young child.

There, I think you're predominantly concerned about children under two months. As an emergency physician, we always used the two-month cutoff. I know that the pediatricians tend to use more of a three-month cutoff for a septic workup in a small child.

So you have those two competing problems, and it seems to me that the best compromise would be

to allow dosage labeling all the way down to two months, but at the same time some kind of cautionary statement about the use of the product in two or three or maybe even four-month-old children, and the need for more careful evaluation by the pediatrician.

CHAIRMAN D'AGOSTINO: I think the way I'd like to handle this question is to have a vote on whether it should be lowered, and then have a discussion on -- If it's yes, then have a discussion on how far it should be lowered.

So from cutting your response into two, you would say yes for the lowering, and then the discussion would be how far. Are there other comments from the Advisory Committee members on this?

So there no questions. I usually miss a hand that's lying somewhere. Then the vote that we'll take -- let's take a vote again to be specific. The first vote is whether or not we think that the product -- can single ingredient products be safely and effectively labeled for direct use in children under two years of age. That's what we're voting on.

All those in favor, please raise your hand. Any opposed? Any abstentions? That's eight to zero again. Thank you.

Now what is the appropriate lower age

limit? Can I ask the question before we begin, that -- and it comes in the response. Are we satisfied with the data in terms of what the appropriate doses actually are? The Boston fever study did bring us a regimen t on what the dose should be, but there was this question about the physicians in the study having very much of the input, and the two months -- I'm not sure we heard a lot of data from six months to two months.

So would people address some of that issue as they talk about this, comment? Any comments or questions? Eric?

DR. BRASS: Again, as a non-pediatrician, it's obvious that pediatricians give recommendations over the phone, and they must have-- there must be a series of recommendations. Part of the reason I have no question voting yes to the initial part is that it is clearly being done and administered through over-the-counter, and it's simply providing more information.

So if there was a consensus recommendation by pediatricians as to what they say when asked, that would seem to be the natural thing to put on a label to be concordant with those recommendations, but as a non-pediatrician, again I don't know if that's true or

what the answer is.

CHAIRMAN D'AGOSTINO: We do need -- I do need some inspiration on this one.

DR. KAUFFMAN: May I?

CHAIRMAN D'AGOSTINO: Yes, please do.

DR. KAUFFMAN: Ralph Kauffman again.

There's no doubt at all, and Dr. Berlin stated it this morning. The Academy of Pediatrics routinely and most pediatric practitioners routinely recommend an antipyretic as a part of the immunization schedule starting at two months of age.

It's also widely used for intercurrent febrile illnesses in children starting at about that age. I agree with Dr. Litovitz. The major concern about mis-self-diagnosis in an infant where an illness might represent something much more serious than just an intercurrent febrile illness is in the under-two age group.

That's where you see the delayed group, B-strep and other serious infections that can -- where the infant can deteriorate very rapidly. That concern dissipates very rapidly after two months, and I think the only reason not to go down to two months is if we thought the two-to-six-month age group represented a greater risk than those above six months, and I don't

think we've heard anything, and I certainly don't know of any reason that suggests -- any data that suggests that that is the case.

In other words, I don't think that we have a reason to believe that the risks are different in the two-to-six-month age group of infants than in the six-to-12-month age group.

CHAIRMAN D'AGOSTINO: Yes?

DR. SILVERMAN: Well, I'm not sure that that's a true statement. I wouldn't be as convinced as you are that between two and four months of age that the ability to mount the appropriate response exists.

As I was taught, and understand the immunology of it was that the passive immunization continues before the immune system begins to work, and I was always taught under six months, worry; under four months, worry a lot; and under two months, it's easy. Do everything.

So I do have a problem with two months, with the caveat, of course, immunizations induce fever. Well, that's to be expected; but my only concern with going down, certainly, below four months is that I think people will overtreat without a fever per se and, as has been brought up many times, fever

is only a symptom. By itself, it doesn't do any harm, and taking that caveat, I think that it really should be strongly recommended that fevers under that age group should be seen by a physician.

CHAIRMAN D'AGOSTINO: Under what?

DR. SILVERMAN: Under -- Well, I personally feel six months, but I don't feel that strongly going down to four, but I would feel quite strongly going under four.

CHAIRMAN D'AGOSTINO: Thank you.

DR. WEISMAN: Rich Weisman. I'm the Director of the Florida Poison Information Center in Miami. I'm a research associate, professor of pediatrics, University of Miami, and I'm here today on behalf of Whitehall-Robins.

I think that there's another side of the coin when you look at the age group between two months and six months, and if you approach it to the susceptibility of toxicity, clearly, the younger the child, the smaller the weight, the greater the likelihood that if a mistake is made, it's going to be to a bad outcome.

I think that this speaks very highly of being able to provide the greatest amount of information to reduce all possibilities that an error

would occur in this group. I think, for that reason, there is good evidence that we need to go all the way down to two months.

CHAIRMAN D'AGOSTINO: I think, if I get the sense of the committee, there's people at the table -- six months is fine. We start running into discussions if we go to four months, two months, but is that the sense, six months, just again to clarify it, and we can pick the six months and lower, but six months is fine.

So Toby gave, I thought, a way of saying that two months up with some sort of further information or further clarification of warning or whatever you want to call it between the two and six months. Do you want to reiterate what you said?

DR. LITOVITZ: I think that the parent of a child between the age of two and six months deserves to have the information in front of them, but at the same time also needs to know that the fever in their child may be a warning or an indicator of something much more serious going on than in a child who is older.

So I think there needs to be, along with the dosing information, special indication or warning for two-to-six-month old children that this fever

could be indicative of something else, and the pediatrician needs to be consulted immediately.

CHAIRMAN D'AGOSTINO: Earl, would that address your concern?

DR. SILVERMAN: I think that that was my concern. As long as it reads the dose, followed by "please contact your physician" would be very reasonable, given that they're going to use it anyway. In fact, this would help.

CHAIRMAN D'AGOSTINO: Can I suggest then that we have an answer that we go down to two months with this added item? Nobody seems to oppose. Thank you.

Why don't we go to number 3: What, if any, other labeling recommendations do you have?

Any further comments on that?

DR. KODA-KIMBLE: We still keep talking a lot about dosing based on age, and I think we had some very good evidence today that dosing should be based on weight. To the extent that the label can begin to reflect that preference, I would advocate that.

DR. TONG: Can I ask for clarification of what we're advocating? Two months?

DR. KODA-KIMBLE: Well, weight, the dosage on weight versus age, because when you start looking

at ages, the weights -- the variation in weight at certain ages is huge.

CHAIRMAN D'AGOSTINO: I think that was the sense of this morning, though, wasn't it, some of the presentations? There was a question about saying weight and then putting age as the first thing that catches your eye, but I think that emphasis is there. It should be.

DR. TEMPLE: Would it be all right if I just made a comment? This has been an issue I've been interested in for a long time.

I really agree that weight would be ideal. The difficulty is that not every parent knows their child's weight and, as much as we'd like them to do that. So we're probably going to wind up having both weight and age on there, but anything we can do to encourage use of weight would be ideal.

In addition, the fact is that these weight ranges and age ranges really aren't that much different. So as long as you use one or the other, you're okay. It's using the right dose that's important.

CHAIRMAN D'AGOSTINO: Thank you. Eric.

DR. BRASS: Coming back again to some of our discussions of last July -- of this past July

about label and comprehension, etcetera, I think, given the issues as we've discussed them, that any attempt to objectively define the best way to communicate when there are multiple dose options, which is the optimal dose, would be very, very helpful, and how that then gets translated to the use of the delivery devices.

I mean, we've talked about labeling of the cups, etcetera. Again, I think that there is a large segment of the population that won't be able to read a five-line table and, if given multiple options, will become confused and will not be able to translate the dose on the table to the delivery device provided them in the package.

I just think that objective data that defines what's the most effective way to communicate that critical information, which is the basis for what we've been spending the whole day talking about, would be very, very helpful.

CHAIRMAN D'AGOSTINO: Well, I think the study that we see the article on where the parents weren't doing the right thing, be it emergency room setting and what have you, is still -- they weren't able to measure out as they were thinking they were going to be doing. You have a comment on that?

DR. LOVELL: Well, actually, there are a number of articles in this packet that were given that addressed the reality of what happens on a day to day practice, and every one of them surprised me and disappointed me on the poor correlation between what's the recommended dose and what the real dose is in terms of 50 percent underdosing and this 30 percent correct on some of the assignment studies.

So I think I agree with your comments directly. It's one thing for us to stand here and make recommendations and for the drug companies to develop labels, but I think it's critically important that objective studies be done to see how that plays out in the real world in terms of can people actually use whatever dosing device we say, and however pretty we make it, does it really turn out to be effective.

So I think that whatever we can do to increase this true information about what happens at the user level is critically important.

CHAIRMAN D'AGOSTINO: Mary Anne, did you have a comment?

DR. KODA-KIMBLE: Well, I also think, if we're going to be lowering the age range, that I would strongly recommend a professional education campaign as well, both for pediatricians and pharmacists, so

that those individuals who are making recommendations of one teaspoonful are also saying in the back of their heads "and make sure you get this specific product that has this specific concentration" or something like that, to avoid inadvertent recommendations.

CHAIRMAN D'AGOSTINO: Earl?

DR. SILVERMAN: Well, I think the issue of actually dosing is crucial, and also being a parent, when you pour out something into a cup, I would be surprised if I was better than a 30-50 percent accuracy also on dosing, over- or underdosing.

If it were at all possible to have a metered type dosing delivery system, as one gets when you go to a bar and they give you a shot of whiskey or something, but could the suspension bottle be built into a metered dose so that it delivers 5 mils or 2 mils and, therefore, the recommendations become something like one metered dose or something like that?

That -- I agree that labeling the cup would be better, and making it easier, but still it's the pouring of it that still becomes very difficult, because it's a small volume into a cup. The only easy part becomes when you use the spoons that just deliver

much more accurately than pouring into a cup, and that may be another alternative -- you know, the spoons that are -- the plastic spoons, not a household spoon.

CHAIRMAN D'AGOSTINO: Very good. Being a grandparent, I have the same concern. Frank, did you have a comment?

DR. PUCINO: I think we're all in agreement that lower dose is safe, and it's being used. I think the only thing I'm still concerned about is once this change takes place, what happens when parents are doing this without the supervision such as we saw in the fever study.

So it would be nice if we could encourage surveillance after a change like that, just to make sure that we're not seeing something unusual in terms of incidence of side effects.

CHAIRMAN D'AGOSTINO: Very good. Any other comments? I think -- You know, this is so critical, as you make this change, the idea of comprehension studies and the idea of surveillance is really critical, especially given all the questions that were left unanswered this morning.

DR. LOVELL: I have a question for the FDA. What's the ability of the FDA to require the industry to actually do studies to assess the accuracy

of dosing by whatever labeling and devices that they choose to use? Can you require a company to come in with that information as well as their efficacy and safety and that sort of thing?

DR. WEINTRAUB: Actually, that's just what I leaned over to Dr. Katz and was about to say to her. I wish we had better control of drugs that are already on the market. Now we can have some control over the dosing devices. We can have some control over that, but a lot of the other things, we have no control over.

We have no control over whether they have to do a label comprehension study once the drug is on the -- has been on the market. So I don't think we can do that. However, we can work with them. We can tell them that, if they don't, the next time they want to change one "a" or "the" in the label -- Now we wouldn't do that, but we can work with them, and by moral suasion help them to see the right way, the necessity for doing those things.

It is a difficult problem. Now a new drug, we can do it.

CHAIRMAN D'AGOSTINO: But if you want to bring the label down to two months, you can ask them to do something?

DR. WEINTRAUB: Yes. That's always -- I was just going to say that to Dr. Katz. We will have the chance to do -- or they will have the chance to do label comprehension studies when the label goes down to two months.

Now what we've got to do is separate marketing studies from these studies, and that's also very difficult, but we're learning how, I hope, and that's what we would try.

CHAIRMAN D'AGOSTINO: Thank you. Are there other suggestions? Put the drug companies out of business with all the studies we suggest and so forth?

Thank you very much. I want to thank the FDA preparations and the drug companies. I thought the presentations were very good, and the questions were comprehensible, and I didn't have a lot of trouble with them, which meant they must be good, and the responses seemed to be fine.

Thank you very much. The meeting is adjourned.

(Whereupon, the foregoing matter went off the record at 2:05 p.m.)