U.S. FOOD AND DRUG ADMINISTRATION

+ + + + +

OFFICE OF THE COMMISSIONER

+ + + + +

PEDIATRICS ADVISORY COMMITTEE

+ + + + +

MEETING

+ + + + +

WEDNESDAY,
JUNE 30, 2005

+ + + + +

The Advisory Committee met at 8:00 a.m. in Room 1066 of the Food and Drug Administration, 5630 Fishers Lane, Rockville, Maryland, Dr. Robert M. Nelson, Acting Chair, presiding.

PRESENT:

ROBERT M. NELSON, M.D., Ph.D., Acting Chair
DENNIS M. BIER, M.D., Member
ANGELA DIAZ, M.D., M.P.H., Member
DEBORAH L. DOKKEN, MPA, Patient-Family Representative
MICHAEL E. FANT, M.D., Ph.D., Member
ELIZABETH A. GAROFALO, M.D., Industry Representative
MARY GLODE, M.D., Member
RICHARD L. GORMAN, M.D., Pediatric Health Organization Representative
PAULA KNUDSON, Acting Voting Consumer Representative
THOMAS B. NEWMAN, M.D., M.P.H., Member
JUDITH R. O'FALLON, Ph.D., Member
MARSHA D. RAPPLEY, M.D., Voting Consultant
VICTOR M. SANTANA, M.D., Member
BENEDETTO VITIELLO, M.D., Voting Consultant
ROBERT M. WARD, M.D., Voting Consultant
JAN N. JOHANNESSEN, Ph.D., Executive Secretary

PRESENT FROM FDA:

PAUL ANDREASON, M.D.

SOLOMON IYASU, M.D., M.P.H.
DAVID JACOBSON-KRAM, Ph.D.
RON KAVANAGH, B.S.Pharm., Pharm.D., Ph.D.
SUSAN K. McCUNE, M.D.
DIANNE MURPHY, M.D.
ROSEMARY ROBERTS, M.D.
ROBERT TEMPLE, M.D.
ANNE TRONTELL, M.D., M.P.H.

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

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

(8:04 a.m.)

DR. NELSON: Good morning.

It looks like everyone is here. So I'll call the meeting to order. And let's start with some introductions before the reading of the meeting statement.

And how about if we start with Elizabeth.

DR. GAROFALO: I'm Elizabeth Garofalo. I'm a pediatric neurologist. I am the industry representative, and I work for Pfizer.

DR. GORMAN: I'm Rich Gorman, a pediatrician in private practice. I'm the public health organization representative, representing the American Academy of Pediatrics.

And today I am serving my last day as the chair of the Committee on Drugs for the American Academy of Pediatrics.

MS. KNUDSON: I'm Paula Knudson. I'm the consumer representative to this committee. I am an IRB administrator at the University of Texas Health Science Center in Houston.

DR. WARD: I'm Bob Ward, a neonatologists and pharmacologist at the University of Utah. And I'm a consultant.

DR. VITIELLO: Ben Vitiello. I'm with the National Institute of Mental Health. I'm a psychiatrist and psychopharmacologist.

DR. NEWMAN: Todd Newman, I'm a pediatrician and Professor of Epidemiology and Biostatistics and Pediatrics at UCSF.

DR. FANT: I'm Michael Fant. I'm at the University of Texas Health Science Center in Houston. My expertise is in neonatology and biochemistry.

DR. RAPPLEY: I'm Marsha Rappley. I'm a developmental and behavioral pediatrician. I'm a consultant.

DR. BIER: I'm Dennis Bier. I'm a pediatric endocrinologist, and I direct the Children's Nutrition Research Center at the Baylor College of Medicine.

DR. DIAZ: I'm Angela Diaz, Professor of Pediatrics at Mt. Sinai School of Medicine in New York City.

DR. GLODE: Mimi Glode, Professor of Pediatric Infectious Disease at Children's Hospital, University of Colorado School of Medicine, in Denver.

DR. NELSON: And I'm Robert "Skip" Nelson. I'm at Children's Hospital of Philadelphia in pediatric critical care medicine, and the University

of Pennsylvania.

DR. JOHANNESSEN: I'm Jan Johannessen. I'm the executive secretary of the Pediatric Advisory Committee.

DR. SANTANA: Good morning. I'm Victor Santana. I'm a pediatric hematologist, and oncologist, at St. Jude Children's Research Hospital in Memphis, Tennessee, and the University of Tennessee in Memphis.

DR. O'FALLON: I'm Judith O'Fallon, Emeritus Professor of Biostatistics at the Mayo Clinic Cancer Center.

MS. DOKKEN: I'm Deborah Dokken. I'm the patient family representative.

DR. ANDREASON: I'm Paul Andreason. I'm the representative from the Division of Neuropharmacologic Drug Products at the FDA.

DR. MURPHY: Dianne Murphy, office director, Office of Pediatric Therapeutics, FDA.

DR. TRONTELL: Anne Trontell, Deputy Director of the Office of Drug Safety, and a pediatrician and epidemiologist.

DR. IYASU: I'M Solomon Iyasu. I'm the acting Deputy Division Director for Pediatric Drug Development at FDA.

DR. ROBERTS: I'm Rosemary Roberts. I am the Director of the Office of Counter-Terrorism and Pediatric Drug Development at the FDA.

DR. NELSON: Thank you. And Jan will now read the meeting statement.

DR. JOHANNESSEN: Good morning. The following announcement addresses the issue of conflict of interest with regard to the discussion of a report by the Agency on adverse event reporting as mandated in Section 17 of the Best Pharmaceuticals for Children Act, for Concerta and all methylphenidate, and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting, and all financial interests reported by the committee participants, it's been determined that all interests and firms regulated by the Food and Drug Administration present no potential for an appearance of a conflict of interest at this meeting.

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.

We note that Dr. Robert Ward, Dr. Marsha Rappley, and Dr. Benedetto Vitiello are participating in the meeting as voting consultants; and that Paula Knudson is participating as the acting voting consumer representative.

We would also like to note that Dr. Elizabeth Garofalo, who's been invited to participate as an industry representative, acting on behalf of regulated industry, Dr. Garofalo is employed by Pfizer.

Dr. Richard Gorman is participating as a pediatric health organization representative, acting on behalf of the American Academy of Pediatrics.

In the absence of committee chair Dr. Joan Chesney, Dr. Robert Nelson will be acting chair for this meeting.

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

We have open public hearing scheduled for 1:00 o'clock today, or 1:30 today.

I would just remind everyone to turn your microphones on when you speak so that the transcriber can pick everything up. And if you have cellphones

please turn them on vibrate or turn them off.

Thank you.

DR. NELSON: Thank you, and the Charge Committee and agenda overview, Solomon.

DR. IYASU: Good morning.

It's my pleasure to welcome you today and bring before you the safety review for Concerta.

Why are we here today? The FDA is bringing Concerta, which is approved for the treatment of attention-deficit hyperactivity disorder to the Pediatric Advisory Committee as part of the regular required reviews of drugs that have been studied in children under the Best Pharmaceuticals for Children Act.

Section 17 of the BPCA mandates that the adverse event reports during the one-year post-granting of market exclusivity be brought before this committee to obtain your input and recommendations.

Concerta received pediatric market exclusivity in December of 2003, and is now brought to the committee for review.

This FDA review, or one-year review, has identified two possible safety concerns, psychiatric adverse affects and cardiovascular adverse effects. These safety issues will be the main focus of the

meeting today.

There are two other approved ADHD drugs studied for children for exclusivity, Strattera or atomoxetine, which was granted pediatric exclusivity in December of 2001, and Adderall XR that was granted exclusivity in October of 2004.

The adverse event reports for these drugs are not the subject of today's presentation.

At this point I would like to give you a brief overview of the agenda for today.

First, Dr. Marsha Rappley from Michigan State University will speak on the clinical experience of the use of methylphenidate products in the management of attention deficit hyperactivity disorder.

She will be followed by Dr. David Jacobson-Kram of the Office of New Drugs of the FDA who will provide an update on methylphenidate cytogenetic effects. This update was prompted by a recent publication by El-Zein et al. in *Cancer Letters* regarding the cytogenetic effects in children treated with methylphenidate. This, as you can imagine, caused considerable press interest, and also interests in the public and clinicians.

And we felt that it would be important to

bring an update as to what FDA assessments have shown regarding this publication.

Next, Dr. Paul Andreason of the Division of Neuropharmacologic Drug Products will provide an overview of the regulatory history of methylphenidate products since the 1950s. So this will provide a context for which ? under which this adverse event review for Concerta will be discussed.

After Dr. Andreason's presentation, we will have a presentation by Dr. Ron Kavanagh from the same division, Division of Neuropharmacologic Drug Products, who will be talking to us about the pharmacologics of methylphenidate.

Next, Dr. Susan McCune of the Division of Pediatric Drug Development, will lay out in detail the results of the one-year adverse event review for methylphenidate products with a primary focus on Concerta.

In the afternoon there will be an open public hearing, and this will be followed by Dr. Dan Murphy, who is the director of the Office of Pediatric Therapeutics, who will provide the FDA's proposed approach and the questions for the committee.

At the end of the day the committee will discuss the information you will have heard, and the

questions that the FDA is seeking your comments on.

We look forward to the discussion, and in particular, to your answers to the questions we have brought to you. We in brief are interested in your comments on our approach to address these important safety concerns.

We thank you in advance for your efforts.

DR. NELSON: Thank you, Solomon.

Now I'd like to introduce Dr. Rappley, who is going to give us an overview of the clinical experience of the use of methylphenidate in the management of ADHD.

Marsha is associate Professor of Pediatric and Human Development, and Associate Dean for Academic Affairs at the College of Human Medicine at Michigan State University in East Lansing.

She's also a member of the sub board of Developmental and Behavioral Pediatrics of the American Board of Pediatrics, and is involved with the Academy's programs in developmental and behavioral pediatrics.

Welcome.

DR. RAPPLEY: Thank you.

What I'm going to present to the committee today is a clinical context for use of medications to

treat ADHD. So this is not a review of the literature, but really to give you a feeling of what it is to be practicing and taking care of children with ADHD, and working with these meds on a day-to-day basis.

I'd be happy to take questions as I present, so feel free to interrupt if there is something that you want to ask me, or if you feel that I've left something out you'd like me to include.

So I'll talk just briefly about source of referrals, where the patients come from, what are some of the major issues in diagnoses. But we'll quickly then get to the treatment options that we have for our children, and in particular, the medications that we use.

Most children with ADHD are managed in primary care, and this includes pediatrics and family medicine. ADHD is one of the most common reasons for a school aged child to visit a pediatrician or family practitioner, and stimulant medications are among the top 10 medications prescribed for children.

So this is really within the bailiwick of primary care for medicine. And in the past, there were people who may have said, I don't do this, I don't deal with children who have ADHD, or I don't

handle these meds, I'm going to ? you have to find somebody else to take care of that.

But really I think the Academy of Pediatrics has gone on record, and the American Academy of Family Physicians has adopted the premise of the Academy of Pediatrics that this does lie within primary care, and it's our responsibility as pediatricians to be well versed and knowledgeable about this very common disorder for children.

Referrals often come from pediatricians own pediatric base, and are initiated by the parents themselves, sometimes in the context of just normal developmental concerns that parents have about their children.

It is a very common diagnosis. People encounter this in their families. They encounter this in their friends. And certainly see it on TV and in the lay press.

So there are often concerns about a child's activity level at all of the well child visits to the pediatrician. And certain referrals come from schools for similar reasons, concern about a child's activity or learning within the school district. And referrals are made from family medicine to pediatrics pretty regularly.

Guidelines come from the American Academy of Pediatrics, and the American Academy of Child and Adolescent Psychiatry, and from some European pediatric groups as well. And these guidelines are quite consistent.

The emphasis that a comprehensive history is key to the diagnostic process, and that information must be taken from important domains of a child's life.

They emphasize the use of standardized checklists, although they fall short of saying that is a requirement to do state-of-the-art assessment, and I think most people would agree that that is the standard of care.

And in fact the Academy of Pediatrics has what they call the ADHD toolkit, which is available to primary care physicians to assist. It has all the tools that they need to do both the diagnostic and the monitoring of medications for ADHD.

Assessing for co-existing conditions is probably the most difficult area in the diagnostic dilemmas for pediatricians, because while pediatricians may accept ADHD as part of their responsibility, accepting things like anxiety, obsessive-compulsiveness, or depression, many

pediatricians are not as comfortable with those diagnoses, and the medications often involved with those.

And so pediatricians often refer out for those evaluations.

Over and over again we see that the current literature emphasizes ADHD as a chronic health condition, one that we have to be prepared to help children and families manage over a lifetime, into young adulthood, and that transition between the pediatrician's office and the adult care setting can be difficult.

Establishment of treatment goals is also very common to these ? is a common feature of these guidelines, so that initiating treatment is based on goals that are clear both to the family and to the physician.

Medication with stimulants to manage medications is a theme of these guidelines as well. The Academy of Child and Adolescent Psychiatry also recommends atomoxetine. Behavior therapy, it is clear from our recent larger controlled studies that there is a role for behavior therapy, cognitive behavioral therapy, for managing conflict between parent and child, or where the child has coexisting psychiatric

diagnoses, or the child with very oppositional behavior.

But when the treatment goal is to improve attention it's medication that does the best job.

Taken all together if you look at all of these guidelines it's my feeling, and it's a point that I tried to make in my article that's in your packet, that they do represent standard of care, and we can refer to a standard of care in dealing with ADHD.

So when we consider treatment for ADHD, if we look at the ? ADHD has the three core symptoms ? inattention, hyperactivity, and impulsivity. And when we consider inattention, medication is clearly the most effective treatment to improve attention. And the medications that have some evidence to support this as methylphenidate, the dextroamphetamine, and when I use dextroamphetamine, I'm including the mixed salt preparations in that group as well, atomoxetine and buproprion.

For impulsivity and hyperactivity, again, medication seems to be the best treatment for this. Again, for oppositional behavior, counseling has a role, and for parent and child conflict counseling has a role. And the combination of the two seems to lead

to greatest satisfaction in parents, and the best treatment outcomes in the long run.

Stimulants are still considered by many to be first-line medications in treatment of ADHD, and as I said in the guidelines from Child and Adolescent Psychiatry they also list atomoxetine as a first line of choice.

And it's because they are so effective in enhancing attention, and they have relatively few side effects. And the experience of course is greater with these medications.

They can provide targeted coverage. They are available as generic medications. And they come in a range of duration from two to four, which would be the shorter acting, to the longest acting of being eight to 12 hours. But still the medicine, by and large, is cleared by the end of the day, which is different in some of the other medications that we use.

And it allows a great deal of flexibility with the stimulants.

Atomoxetine, as studies show effectiveness is more in the range of 50 to 60 percent, and the side effects profile is similar to that of the stimulants. It does provide 24 hour coverage, takes a longer time

to reach effect.

Buproprion probably has fewer studies of any of these medications, and it has more serious side effects as well. It has the additional role of an anti-depressant effect which some people are also noting in the use of atomoxetine, and I think studies are underway to examine that role.

Buproprion provides 24-hour-a-day coverage and takes a longer time to reach its effect as well.

So stimulants are the medication that are chosen for most children and teenagers with ADHD. Methylphenidate and dextroamphetamine products have similar profiles. Dextroamphetamine products have slightly more side effects, albeit mild side effects.

Then there is the concern about the Adderall XR product recently withdrawn from the Canadian market, that concern being among parents who have come to talk with physicians about these medication choices.

And also the warning about the use of this particular medication in children with cardiac conditions.

Because these medications have such similar profiles, parents may have preferences about this, and most pediatricians are happy to respect that

preference, and use whichever medication the family is inclined to use.

Again, many parents come very well read about this condition. They're very knowledgeable about their medication choices. They have talked to people in their school environment and their family and the community, so they may in fact know almost or as much as the treating physician when they come with their child to discuss these things.

Setting target outcomes is very desirable because in working with ADHD it's very easy to get lost, to get mixed up about what you're treating, what you're not treating, what was the baseline condition before you started medication. Are things really better? Or did we raise the bar, and now we have higher expectations, so that things are better, but they're not quite as good as maybe the family would like them to be.

So it's very important for the practicing doc to establish a baseline condition. And what are the things that are the most problematic for the family, and what is it really that they would like to work on.

In the area of inattention, this often involves work completion. It's a very common

complaint that the child doesn't finish the work. They don't finish the work in school, they don't finish the work at home, homework takes an inordinate amount of time.

It's very common for people to say that they work three, four, five hours on homework a day, and that this is a major source of conflict between child and parent.

And this is what they want to fix. This is what they want to improve, they want to take the pressure off that situation.

Things like spelling tests, especially for younger children, it's a very common report that the child gets the first two or three words correct, and then the rest of the words are written all over the page, or maybe a couple of letters, or you can see that the child's attention has wandered almost graphically in the way that they complete the spelling test.

Same is true with some of the timed math tests, especially addition and subtraction and times tables that come as a sheet that the child has to complete at their desk within a certain amount of time. All the other kids will be done, and this child might be doing a very good job on the first few

problems and then again it's almost a graphic display of the attention wandering away from a task.

Fluidity of thinking and writing is an important concept, particularly as the children get older. Mel Levine talks about one of the most startling images he had as a child tried to explain the problems with ADHD was copying transparencies. The teacher would put up the transparency, and the child was supposed to take notes, or get a take home message from the transparency, write it down, and then look up for the next transparency.

And the child with ADHD has to concentrate on what is presented on the screen, has to concentrate on writing it on the paper. And by the time they go back up they've lost it. They no longer have the train of thought. The teacher is doing three transparencies ahead. Everybody else seems to get it, but the child with ADHD is still struggling to keep up.

And they learn very quickly that they get lost in the first few minutes of such a presentation. So sometimes talking to a child in the office about that experience and how that changes over time can be a way of making some targeted and measurable outcomes.

Hyperactivity and impulsivity is often not

expressed as a problem from the child's point of view. They don't really see that this is a problem. And a problem is identified by and large either from parents or teachers.

Sometimes it interferes with their friendships, and so those are the kinds of things that they talk about. No one likes them. No one will stand in line with them. Nobody wants them on their team.

So some of the measurable types of outcomes that you can use, and that we use in the office, are how many calls from school. It's very common for parents to say, I haven't had a call from the school in a month so I know the medication is working.

So this might be a parent who had to go a couple of times a week to pick up their child from school or to come to school to discipline the child.

Episodes of detention can be used as a measure. The ability to engage in the activities that we think of as normal developmental tasks in childhood, the social activities such as Cub Scouts, sports, and I'm not talking about very highly regimented intense kinds of experiences, but the kind of experiences we want for all children, that they are

with friends, that they feel successful with their friends, that they are able to make things and do things and establish friendships outside of the school setting.

I think one of the most compelling stories I've heard from my patients is a father who told me that when he took his son to the Cub Scouts meeting they would not answer the door. And they would look out, they would see that it was him, he was there with his child, but they would not answer the door.

So it was a very big accomplishment for the child to be accepted into the Cub Scout meeting, and that was due to how we were able to accomplish that using medications not only then just for school day but for this other important dimension of a child's life.

Quality of relationships is important, too. It's more difficult to measure. It's much more subjective in the kind of report we get back. The children often talk about teasing from their peers because they're different, they cause trouble. I mean they may or may not be geeky. They might be a bully on the playground. But they very often are without the kinds of friendships that we want for children.

Other people do not want to play with

them. They feel isolated. Teachers talk about being in a vicious cycle where they are constantly scolding and providing negative messages to the child. It's not where they want to be. Teachers may express frank dislike for a child.

I've had at least three teachers tell me that the child cannot come back to the classroom until he's on medication.

Now, at first I got really angry about that. But then I thought, well, that doesn't help if I respond in that way to the teacher on the telephone. So I say, well, you know you can't say that. You know you can't really say that the child can't be in the classroom. Then invariably there is an outpouring, well, he ruined the last picnic, and he did this and he did that. And the teachers are pretty desperate by the time they are telling the doctor that they must prescribe medication.

So generally that's not a drug-seeking behavior on the part of the teacher. I see that as a mark of desperation when teachers are reaching for that.

And the other thing we can watch for is engagement in the learning activities. Children who have to be disciplined constantly, children who have

to have separation, and isolation, from their peers, they're often not able to engage in some of the smaller tasks, some of the things that are more fun in the classroom.

And if they cannot engage in the learning activities, they're not going to learn. One of the things we have to be very careful about as physicians is that we do not talk to parents and kids, whether they're school age or teens, about attention problems, if indeed they are suspended from school regularly.

The goal there is to get the child back in school and participating in school, and then we look at modifying the attention. Hopefully that will come, but that goal is not as important as getting the child engaged in that daily developmental activity that is appropriate for the age, and that is attending school regularly without discipline and suspension.

Parents also, it is not uncommon for parents to cry in the office about the experience of parenting a child with ADHD. Very often it brings back memories of their own childhood and the conflict and disappointment that they had, that they felt struggling to learn with their own problems with ADHD. But it almost always relates to ? this is not the experience of parenting that they want. They do not

want to be scolding their child from sunup to sundown. They do not want every interaction to be one of limit setting. They want to move to a point where they can have a positive interaction with their child.

They want time for affection with their child. They want time to provide support to that child.

Siblings, this can be a place of very fierce and intense anger. It's often an outlet for solving the problems on how one expresses anger, finding appropriate ways to express anger, finding your place in the hierarchy of the world.

And for the children with ADHD, they can be very irritating to their siblings. That can be a very negative experience, and there may be more than one child with ADHD in the family, which is also a very difficult situation.

So sometimes we work on decreasing the reactivity, so the child with ADHD is not so easy to tease, does not respond so impulsively, and likewise, does not impulsively provoke others.

In severe ADHD safety concerns may be the priority. So for example it's not uncommon for parents to tell us that they do not take this child out of the house; that they walk this child to the

school bus. The child has a special seat belt or restraint that is used on the school bus. Someone meets the child at the bus and walks them into the school.

Sometimes people use phrases like, hands-on supervision, or two-on-one supervision. Children with severe ADHD are difficult for one adult to manage.

And so we may be looking first then at the issues around the child's safety, running away, impulsive, running out of the house.

It's not running away in the same way as one trying to get away from an unpleasant experience, but curiosity, poor judgment, impulsive decision making, that leads young children to climb out of second story windows, to be wandering the streets at 2:00 o'clock in the morning in the middle of the winter in their pajamas. These are not unusual things that parents describe to us in children who have severe ADHD.

It's really important that the treatment goals make sense to the child. And even a young child can understand that we are working to help things be better for them.

And given the opportunity most young

children, as young as five and six, can give words to the things that they want to be different in their life, too. And it may be that someone will sit next to me, that I don't have to sit in the back of the room with my chair turned to the wall. It might be that I get to be on the team at recess, or I get to go out on recess, because very often a restriction of recess is a disciplinary measure, or it's used to provide time to do schoolwork that wasn't previously done.

So young children can give voice to what they would like to gain from the treatment. And it's in the pediatrician's best interest to seek that out and to listen to that. Because this is a person you engage with as much as the parent. This is the person who has to take the medicine. And so if it doesn't make sense to the kid, then you have a hard road to travel.

Treatment goals also have to make sense to the parents. For example I had one parent who said to me, why don't I get any benefit from this? How come I give the medicine, kid goes to school, and I do all the work, I bring him to the appointments, I make him take the medicine, I pay for it, but the teacher gets all the benefit.

So that was a situation in which I really had not had a clear discussion with the parent about what they hoped to have out of treatment.

And it's also true that oftentimes parents are reluctant to say that they would like their child to be different. They very much want to say that I tolerate this child. It's okay with me that he's irritable, he's hyperactive, he's all over the place, he's hard to manage. I just want him to be okay in school.

And then when we see that we can get him a little bit okay in school, amid things can be better, then maybe it's okay for that benefit to be gained at home as well.

So when we think about medications now, our first choice about medication, our first decision point, really is, do we want a longer acting or a shorter acting medication. And this really needs to be linked back to the treatment goals. That's why treatment goals are so important. They will help us decide about which avenue to take first, and there are many, many options right now. And they will help us decide whether or not we're on the right track, and if the medications we're using are effective.

So the benefit of long-acting medicines,

of course you don't have that midday does. So particularly the older school aged child and the teenaged child, not having to take a dose in school is a big improvement to the landscape for ADHD.

It also can be a good thing for compliance in a child who is able to swallow the larger size pills or tablets that come with the longer acting preparation.

The shorter acting preparations allow targeting of certain times of day, and this can be particularly important in a younger child who might be in a half a day program, and the parents really are fine with the child's level of activity at home, but the child needs to be more engaged in what's happening at school, so a short-acting can be used to cover those hours.

And sometimes a short acting can be used to moderate the effect of the side effects that are experienced with these medicines.

When we choose an initial product it's largely determined by the insurance coverage. And most of the insurance, at least in our area of Michigan, are highly restrictive of our choices in this area. They may choose one long-acting product. Occasionally we have an insurance company that does

not allow any long-acting product, and then there is a lot of complaint from the consumers and generally that has changed.

But in our state at least most of our insurance companies are covering only one long-acting product.

And the difference between the generic short-acting and the long-acting can be greater than $100, and in some cases, for higher doses of the products, it can be up to $200 ? 300 that parents are spending.

One of the things that we sometimes lose sight of unless we are also going to the pharmacy with our own prescriptions is that there is a copay on every prescription, and at least in Michigan we must write a separate prescription for a 10 milligram, for a 20 milligram, for a 5 milligram. If we are using a combination of tablets in that way, the parent pays a copay for every one of those prescriptions, and we're now looking at copays of $40 ? 50 commonly for meds that are brand name, and they are a little bit less for the generic, sometimes in the range of $20 for the generic meds.

So these are things that may influence our choice of medication. And we ? it's very

difficult for us to say that the brand name is better for the child. It's better in the quality of life arena, which does not hold a lot of weight when you're talking to the insurance company.

When we choose an initial dose we want to go for the lowest dose that is effective. However, when I started working in this area in the '80s we routinely started at low doses no matter ? pretty much no matter what the presentation of the child was, and then we gradually worked up. We did not want to be caught using a higher dose than we needed to use for these meds.

But one of the benefits of our randomized controlled studies, the very large studies that have been, is that they show us, they give us information about what does really are most likely to work for children.

In the clinical study we do not use a milligram per kilo dose. We look at the younger child, the child who is very slight in terms of perhaps a lower percentile in weight and height, and the child who is primarily inattentive and does not have the hyperactive or impulsive features.

And we would choose a lower dose range for those children to start, and then titrate up.

For the older child, or if symptoms are more severe, we start at a moderate range. I think very few people would start out with a high dose, but we would start in the more moderate range.

I'll talk about what some of the doses I would consider from a clinical setting to be lower dose and moderate and higher dose.

When we think about dosing, we remember that the dextroamphetamine products are higher potency than the methylphenidate products, so we're prescribing usually a lower milligram dose to get equivalent.

And sometimes that takes some explaining to parents. There is a lot of mythology that you have to overcome in terms of the education around these medications. And one of them is that a dose of 10 milligrams or 15 milligrams or 20 milligrams is not morally superior to be at the 10 as compared to the 20. But yet we are trying to arrive at what works best for the child and does not cause side effects.

In dosing intervals we can look at two to four, sometimes five times a day, and especially in the very young child who seems to metabolize these medicines quickly.

In the longer acting one time a day is

often effective. On the other hand we often use one longer-acting in the morning and then a shorter acting generic product of the same medication in the later afternoon or early evening for some of the either homework or kinds of activities that kids do in the evening.

There is not any evidence to support mixing products so using methylphenidate long acting and then the dextroamphetamine short acting in the evening, or ? and it's very easy to stay within the same family.

There is not evidence really to support that. But also, it's very easy then to get mixed up about what meds work best for these children. And a good principle is to use one of the products, and to use it at an appropriate dose. And if the child does not respond, is in that 20 percent category who may not respond to this medicine at the appropriate dose, or has side effects without getting benefit, then it's time to change to another medication altogether.

So with lower doses or the short acting, I would consider that the five to 10 milligram range for methylphenidate and five milligrams for dextroamphetamine products, longer acting 10 to 27, and five to 10 for the dextroamphetamine products.

Moderate doses, we're giving more in the range of 20, 10 to 20 for dextroamphetamine products, and then in the longer acting, up to 54 milligrams, depending on the product being used, and 40 milligrams of the dextroamphetamine products.

When we talk about higher doses, this is all subjective. And I'm sure that if we had a group of pediatricians and child psychiatrists, we would sort of more or less agree, but we would each have our own individual way of viewing this.

At higher doses on the short-acting, per dose, would be something greater than 20 milligrams per dose, or greater than 60 per day; 60 per day is really what's in the package insert as an appropriate maximum dose per day. And in most of the referral clinics, be that in developmental behavior and pediatrics, or in child psychiatry, we are commonly working with doses higher than 60 milligrams per day, 80 milligrams, 100 milligrams, per day.

And of course those are the children with the more severe symptoms. They're less responsive to the lower doses, and often the decision point is a higher dose of methylphenidate or adding a more ? a medication that has more side effects such as an atypical anti-psychotic.

Longer acting than the higher dose categories are greater than 72 milligrams for the methylphenidate products or perhaps 40 for the Dexedrine. And then that's a little bit different in the younger children.

The guideline really is to start with a dose that is likely to be effective, and then titrate it up to effect without side effect.

So that requires monitoring, and this is where I think we need more research, and we need more guidance. People ? we need to come to the point where we can say there is a standard of care for monitoring for these children, because there are a large number of children who get prescriptions for a year at a time and who do not see a medical practitioner.

But we do not have ? it is not well studied, so we don't have good guidance around this. Many people recommend that it's every three to four months. It's what I recommended in my review.

This allows monitoring for both effectiveness and for side effects.

If intervals are longer than every four months, there are a set of things that tend to happen. One is that the meds continue but it's not effective. So you might have a child taking 10 milligrams of

methylphenidate but it's not working very well, and you don't get that feedback because you don't see them in the office, and they continue on this through a whole school year. So they're taking a medication that basically is not helping them, and that's not necessary.

Sometimes that leads people to say, this medicine doesn't work for me, because they never really had careful titration to an effective dose.

And it may lead to them turning to medications that actually have more side effects and are more difficult to work with.

The other reason is that there is a potential for mild side effects to be tolerate unnecessarily. So if a child does not gain weight, and we'll talk about that in particular in a few minutes, or if a child is having headaches or stomach aches with this medication, we can generally moderate that by either dose or timing. And there is no need for the child to make that tradeoff, to tolerate that side-effect to get the benefit from the medicine.

Very young children and children with coexisting conditions, they really need visits at least every three months. There is more diagnostic challenge in this age group. There is that wide

developmental range of when the child will gain the ability to master their activities, to marshal their attention, to stay focused. And for the young child we need to allow that opportunity. And we don't understand that if we're not in contact with them frequently.

There are more side effects in the young children, so they have to be monitored more carefully.

And then there is the possibility of under treating the coexisting conditions, either perhaps a depressive order is masked by the hyperactivity and people are fine that the child is less hyperactive, but no one is attending to the mood disorder.

There is also the possibility that our diagnosis was wrong. And every time we see a child and follow up we revisit that. We ask ourselves, is this the appropriate diagnosis? Do we have the appropriate information? Do we need to be carrying out other assessments with this?

So in monitoring at all visits we look at blood pressure, pulse, height, and weight. Those are really the requirements for every visit for follow up. And we inquire specifically about these common side effects: loss of appetite; headache; abdominal pain usually expressed in a stomach ache in a young child;

changes in sleep; tics; mood changes; irritability; what is referred to as a rebound phenomena. Almost all of these are very amenable to alterations either in the dose or the timing.

Appetite suppression is one of the major side effects we have to work with. And we can expect it to occur in about 80 percent of the patients that we're taking care of.

But for most children and families, just awareness of this as one of the major side effects prevents it from happening. And if it does start to happen we can catch this with frequent visits, and we can give the family the information they need to address that.

This problem is generally more pronounced in younger children.

But there are children who have to find their own food. For example, I had a six-year-old child who was being sent home from school regularly because of the activity level and was not a good social circumstance, and sometimes that's the case. ADHD crosses all socioeconomic and all social strata, so we will find this in families that are chaotic and poorly organized, and we'll find this in highly organized and higher functioning families as well.

But for this six-year-old who had not gained weight, I told his mother that he would have to come off the medication, and she began ? she was a very young person herself, she was 18 years old. And she began yelling at the child because he didn't eat, and he should have found the hot dogs that were in the refrigerator.

So there is not an adult, really, getting food for this child. This is something I had to come to terms with, and in pediatrics we're all very familiar with this scenario, that sometimes we have to focus on the child when we don't have a competent adult who is there caring for the child.

In those situations it's very difficult to work around the appetite suppression, because the child needs more than just access to food. Some families are very rigid. You have to eat what's set before you. If you don't eat at mealtime, you don't eat. That's the deal.

That doesn't work with these kids, because they are often not hungry at mealtime. They'll be hungry just after everybody else has eaten, before they go to bed. Parents feel that's manipulative. Maybe it is. Maybe they're going after Debbie cakes, and that's not the way you want to get good weight on

them.

But these are difficult families to work around this side effect as well.

Some children fail to gain weight, and this is not apparent until their height is affected. The pediatric endocrinologists tell me that one of the most frequent diagnoses now in their clinic is short stature secondary to use of stimulants. And so what we need to understand is, this is really ? and that's anecdotal; that hasn't been studied as far as I know ? but what we do need to study and understand is, is this really an effect of the medication, or this a failure to monitor, and a failure to pay attention to those things that we can do something about?

Headache and stomach ache generally are associated with not eating. A lot of kids go to school without eating. Then they're not hungry at lunch time because the medicine cuts the appetite, and they'd rather play anyway. So if your choice is standing in line for food that you're not hungry for, or going outside to play, most of them go outside.

And so we have to talk about having a good breakfast. And even though the package insert always say, take it on an empty stomach, taking it with food may get around this side effect.

Sleep onset: It's very important to look at what's the baseline as the child is coming in, because this is often reported as a side effect when actually it's part of the child's baseline condition.

And recent research is pointing in both directions, that sleep onset is a problem with ADHD itself, and not just the medication, and other studies have shown that it can be associated with the medication.

Usually this is responsive to timing of the last dose or the amount of medicine in the last does.

Tic disorders, it's also important to establish baseline. And to also understand that tics may not be recognized in a family. People may not ? teachers may not recognize that a child is having what we would understand as tics. And this is no longer a contraindication to treatment with stimulants.

Mood changes, irritability, this does occur for some children at modest doses, but it's usually associated with higher doses. Some children are more sensitive to this effect than others and do well if they're switched to the other stimulant. So they may have this effect on methylphenidate, but you put them on a dextroamphetamine product and it doesn't

happen, and the reverse is true.

It's always important to look for other reasons for irritability for a child as well.

But I think it's also very important for us to maintain that it's not a fair tradeoff, to have a child be more attentive, more focused, accomplishing more in school, but not a happy child. And that we need to explore.

Rebound, some people say this doesn't exist, that it's the increased irritability that's noted when the medication wears off. It comes at the end of the day which is an irritable time for many people. Some places they take siestas at that time of day, because that's a hard time, 3:00 to 5:00, it's a hard time for people to cope. Kids try to be good all day, they're coming home, they can let down. It's safe to be angry. It's same to be themselves, hyper, impulsive, at home.

Again, it could be associated with not eating. It could be associated with things going on with siblings. But it may be responsive to inducing a kind of tapering of that dose by lowering the doses over the course of the day.

It was one of the things that people thought might be addressed with the longer acting,

that this may be less, seen less frequently. And I haven't seen whether that has really been specifically studied to get to see whether that has been a benefit of the longer acting preparations.

How often do you change the dose? A dose can be effective for one or two years. People can be on the same dose of medication for many years. It's not necessarily increased every year. Parents always worry, do we need to increase the medication because the child is getting bigger? And again, you have to look at the effectiveness and the target symptoms.

Summer, holidays, weekends off, go back to why the medication is being used in the first place, and that determines then whether or not the child should be off for holidays or in summertime. This may be an important way to manage the weight gain issues, but if many of the issues have to do with quality of life and friendship, that's an important part of summer as well as school.

How long to treat? When I first began seeing patients we had access to placebos that were provided by the pharmaceutical companies. Those are not available anymore. It's a cumbersome thing to organize the clinical double blind placebo where the doctor, the patients, the teacher are blinded, and

you're trying to determine whether or not this medicine works for a child. It's expensive. It's not covered by insurance. The family has to bear the cost of that.

But it also may not be necessary, because we do have years of research on thousands of children that show us these medications are effective.

Adolescents often want to stop their medication. I think that that's an important developmental phenomena. We understand that as pediatricians, and we try to work with that and make deals with the family and the adolescent. Okay, let's try to go off during a low stakes period of time, and then we have to make agreements about living with the outcome. Parents agree not to pressure for meds if the child ? if the teen does okay, and the teen agrees to take the meds if the grades take a dive.

It's very important, one of the most important things we do as physicians is teach our young people about their condition and about how this medicine helps them, and how they will use that when they leave this sort of sheltered environment of the school and the pediatrician's office and move into the world of work, the world of college, where pressures are different.

It's a better world, because they can play to their strengths, which they can't always do in school. But it's also a more difficult world because nobody is there to remind them to take their medicine. They have to make difficult decisions.

I have ? actually I have a substantial number of kids who are ? of young people who are in their 20s now who come back and ask me, they want one visit to talk about working night shift in production at the Humvee factor here in Michigan, and how should they work their medicines around this production line? And what are the safety issues?

So helping people transition to young adult life with this condition and taking these meds is a very important part of what we do.

More than one med. Bottomline here is not for uncomplicated ADHD. There is not guidance around this. Generally when we use more than one med, it's because there is more than ADHD going on.

Challenges are that it's difficult to know what's helping, it's difficult to know what's causing a side effect, and it's difficult to anticipate interaction.

Stimulants are one of the most common ? stimulants and the SSRIs are the two medications that

you find in combination with other meds most often. So it is something that we encounter often in the office, and as physicians we're all blaming the other guy. You know, they sent him to me with all these meds; I didn't do this.

So somebody, we have to share the responsibility for making decisions about placing children on more than one medication, and then finding appropriate ways to manage that.

That's the end of my presentation. Thank you.

I'll take questions.

(Applause.)

DR. NELSON: Thank you, Marsha.

Thank you for setting our discussion into a clinical context, and the importance of that.

My preference would be to try and move on. If there are burning questions about this that you think are relevant to our discussion of the drug use, if anyone has any, as opposed to differences in clinical management and pediatrics, which I'm sure there would probably be plenty of a discussion if we wanted to.

Are there questions that people feel need to be asked right now?

Okay, thanks.

DR. RAPPLEY: Thanks.

DR. NELSON: Our next presentation is on the cytogenetics, and Dr. Jacobson-Kram will be presenting that ? yes?

DR. JACOBSON-KRAM: Good morning.

Basically my presentation is to discuss this publication which was published online several months ago, and now has come out actually in print.

And it looked at the cytogenetic effects in children treated with methylphenidate and this study was performed by a group at the University of Texas.

The study design examined three endpoints in 12 children that were diagnosed with ADHD. Blood was drawn before and after three-month treatment with methylphenidate, and the endpoints that this group looked at were sister chromatid exchanges, chromosomal aberrations, and micronuclei.

The therapeutic doses that were used ranged from 20 to 54 milligrams per day.

So what are sister chromatid exchanges? I wasted much of my youth researching this particular endpoint. These are reciprocal exchanges of chromatid arms that are visualized in metaphase cells that have

undergone two rounds of DNA replication in the present of the nucleotide analog bromodeoxyuridine.

And while the mechanism of SCE is still poorly understood, increases in their frequency are generally indicative of DNA damage.

So this is what a sister chromatid exchange looks like, and this cell has quite a large number of SCEs. And you can see that there is differential staining in the two chromatid arms. So one chromatid arm stains dark, and the other one is light. The light staining chromatid arm is completely substituted with bromodeoxyuridine, and every place where you see a reciprocal switch in the staining intensity is the site of a sister chromatic exchange.

So basically what's happened is, the DNA helix has switched over from one chromatid arm to the other. If it's a perfect switch it should have no genetic impact. That obviously can't be seen under the light microscope. If you've missed by a single base, obviously, then you'd have a friendship mutation.

So what are chromosomal aberrations? Chromosomal aberrations represent unrepaired or misrepaired chromosomal lesions that are visual under the light microscope. And the same processes that

give rise to these events are the ? are ones that are associated with chromosomal alterations resulting in cancer. And classical examples are Burkitt's lymphoma or B-cell lymphoma.

So these are breaks in chromosomes and then inappropriate rejoining. And here are some examples of what they look like. And for those of you who are cytogeneticists, you probably realize that these are not human chromosomes, these are hamster chromosomes which are typically used in assays simply because there are few of them, they're large and they're easy to visualize. But basically they show the same thing.

So in the upper right photomicrograph, these are chromatid gaps, and you can see the small discontinuities in the chromatid arms that are smaller than actually the width of the chromatid arms, so they're classified as gaps.

In the lower left, in the circle on my right, this is a chromatid break. So you can see there is a large discontinuity in that chromatid arm in the circle.

And then further to the left this is a triradial. This results from chromosome breakage in two different chromosomes, and then inappropriate

rejoining of the sticky ends of the chromosomes. So again, these are characteristic kind of chromosomal aberrations.

And the one in the lower right, this is a dicentric. Again, this results from breakage in two different chromosomes and then inappropriate rejoining, so that now this one chromosome actually has two centromeres. And this is a signature aberration for exposure to ionizing radiation.

What are micronuclei? Micronuclei result from acentric chromosome fragments or whole chromosomes that are left behind in the cytoplasm after mitosis. They are visualized in binucleated cells that have been blocked for cytokinesis, and they are indicative of chromosome breakage or nondisjunction.

And here is what that looks like. The cell on the right is, this is a binucleated cell, and it's normal. The one on the left with the arrow, this is a micronucleated cell. So this little fragment there in the cytoplasm, this is indicative of a piece of a chromosome that has broken off and been left behind in the cytoplasm, or maybe an entire chromosome that dislodged from the mitotic spindle apparatus and was left behind in the cytoplasm.

So what is the significance of these cytogenetic endpoints? Chromosomal aberration frequency in peripheral blood lymphocytes in humans is an independent risk factor for cancer. So if you look at cohorts of people and you measure their frequency of chromosomal aberrations, those with the highest level of aberrations have a higher risk for cancer.

Now we can't say that on an individual basis, but as a group people with lower ? groups that have lower frequencies of chromosomal aberrations have lower risks for cancer.

So if the data in the El-Zein paper are reproducible, this would suggest that patients taking methylphenidate may be at increased risk for cancer.

So what else do we know about the mutagenicity and carcinogencitiy of methylphenidate? Most of everything else we know about it is actually pretty reassuring. There are no structural alerts. So if we look at the structure of the molecule, nothing jumps out at us that says, potential mutagen or carcinogen.

The metabolism of the drug is qualitatively similar in humans and animals, although there are quantitative differences. So what that tells us is that the data that we get from animal

studies are probably applicable to humans.

And what is know is that in a rat carcinogenicity study, methylphenidate gave a clear negative result, and it was also negative in a mouse p53 transgenic study; p53 straight is the one that's commonly used to test for compounds that are genotoxic.

It did induce liver tumors in a mouse carcinogenicity study. However mouse liver tumors are very common, and it's the kind of lesion that we generally don't get that excited about.

Aside from that we know that methylphenidate is negative in Ames assay, which is a bacterial reverse mutation assay. It's negative in a mouse lymphoma gene mutation assay, which is an in vitro Mendelian gene mutation assay. And it's also negative for chromosomal aberrations for micronuclei in rodents.

There are some positive or equivocal results for in vitro chromosomal aberrations and sister chromatid exchanges. Review of pharmacy and medical records of over 140,000 patients found actually fewer cancers ? cancer cases than would be expected. So again, everything else we know about this drug is fairly reassuring.

So these are the data from the El-Zein study, and you can see chromosomal aberrations in the ? before versus after. There is very highly significance increase on the frequency of aberrations. You can see that the frequency of sister chromatid exchanges is very dramatically increased, going from six to 26, and also the frequency of micronuclei increases, all these are highly statistically significant.

Now if you look at the individual data, not only are the averages increased for the endpoints, but these are the data for the individual patients, and for every patient and every endpoint there was an increase in the endpoint from before they started taking the drug to three months into taking the drug. So we found this to be obviously quite concerning.

But we also had some questions about the El-Zein study. There were no placebo controls. They are not always included in these longitudinal type studies, because each patient essentially is their own control.

The confounding factor here is time, because a significant amount of time can pass. Reagents can change, things can change, and as a result, we're not always sure that the increase is the

result of the drug as opposed to some change in the technique that results over time.

The authors also used some unusual data presentation which are typically not used in these kinds of studies. For example they talked about aberrations per cell instead of percent of damaged cells.

This is an important point, because sometimes you can get one cell that has a lot of breaks in it. And so just by including that, that has a big impact on the aberrations per cell. But if you look at cells with aberrations, then that is taken in context.

They also expressed the SCE frequency as total SCEs in 25 cells. This is something that I have never seen in any publication before. And what was particularly concerning is, there were six individuals that had zero SCE per cell. To me, this was the really dramatic finding of this paper, because a human being with zero SCEs per cell has never been previously reported. (Laughter.)

In fact, if you're wasted your youth on this endpoint as I did and looked at hundreds of people, it's rare actually to find a single cell that has no SCEs. You can occasionally find one, but it's

like finding a four-leaf clover. You get very excited about it. You call your colleagues over and you show it to them.

Finding 25 in a row is unprecedented, and then finding six people with 25 in a row, it's like you know winning every lottery in the country. It's just unprecedented.

So we had concerns because of that. So we asked to site visit the group that did the study. And so in fact a group of us with representatives from the National Institute of Environmental Health Sciences, also NICHD, FDA and EPA site visited the University of Texas on May 23rd. We reviewed patient selection, the methods that were used, raw data, and the slide evaluation.

So the observations at the site visit: the investigators were extremely cordial. They were cooperative. They answered all our questions. We found that there was good concordance between the raw data sheets and the data in the publication.

In studies like this it is very important that the slides are evaluated blinded, that is, so the observer doesn't know what the treatment was. And in fact the slides were scored in a blinded fashion, but the same technician coded, evaluated, and decoded the

slides. So that is a bit of a problem, although I don't believe that the technician actually knew what the treatment was. It would be a lot of numbers to keep in your head, but it's not the best way to do it.

We also chose a number of slides at random to look at, and we found that they had low mitotic indices which makes them hard to score, and that there was poor differential staining for the sister chromatid exchanges.

So what impact did it have? If we look at what is the impact of bad differential staining, this is illustrated in these slides. For example this is a good preparation, and you can see that the differential staining is quite good between the dark and the light arms. So it's easy to visualize the sister chromatid exchanges.

If you have a bad preparation that's shown in the photomicrograph next to it, it makes it very hard to enumerate the SCEs, and this may actually be how you come up with people who have zero SCEs per cell.

Having said that, if even though there were bad preparations, if the slides were scored blindly, there still may be a signal in there. The signal may be somewhat camouflaged by the poor quality

of the preparation, but if you have no observer bias, and they're all kind of equally flawed, there may still be some significance to the observation.

So we're still taking this quite seriously.

So we have some ongoing efforts to assess methylphenidate clastogenic potential, organized under BPCA. El-Zein, et al., the original authors, are seeking funding to perform a larger study with 100 informative subjects. NICHD, NIHS, and Duke are collaborating to reproduce the El-Zein study in North Carolina.

CDC has developed a protocol for a cross-sectional study that incorporates cytogenetic endpoints. NIMH will assess stable chromosomal rearrangements as part of an ongoing cross-sectional study.

So these patients have been on methylphenidate for a long time. And as a result, by looking at stable chromosomal aberrations, using fluorescent in situ hybridization, you can kind of integrate the chromosomal damage that has occurred over a long period of time by assessing the endpoint, and using that method.

The Division of Neuropharm Drugs is asking

IND holders to assess clastogenic potential as part of their clinical trials. The National Center for Toxicological Research will perform experimental studies in non-human primates, and also in transgenic mice.

And other drugs that are used to treat ADD and ADHD will also be studied. We expect that the first results from these studies will be available in about a year. So I'd be happy to answer any questions.

DR. NELSON: Thank you.

Let's go to questions from the committee.

Benedetto?

DR. VITIELLO: A question more about the methodology of the test actually. You said that it had been shown to have validity, predictive validity, that aberration, cytogenetic changes actually predict an increased risk of cancer.

Still my understanding is this methodology is not routinely used in drug development. It's relatively simple, it's in vivo, it's in humans, it's low tech. Still it is not part ? you listed a lot of other tests. Why is that?

DR. JACOBSON-KRAM: Yes, it's a real good question. I've actually been an advocate of including

it.

Now we do, as part of drug development, we do chromosomal aberration studies in human cells in vitro, and also in animals. But we don't do it as part of the clinical trial.

And I think the reason is, sponsors don't do it, one, we haven't insisted on it, but also, let's say you do see an increase. What do you tell the participants in the trial?

You can't say that your individual risk is increased, even though we've seen an increase in aberrations for you. Because we can't talk about individuals; we can only talk about a group.

So then there are issues of what do you tell participants. What are the liability issues associated with seeing such an increase?

DR. VITIELLO: Isn't that the same on any safety test, that you can may find a group difference that applies potentially to all the patients who receive the medication but not necessarily to the individual level. I don't see the difference.

DR. JACOBSON-KRAM: Well, I think the difference here is, A, you probably are thinking about doing this in healthy volunteers in phase one studies, and also, the health impact would not be seen

theoretically for many, many years, probably decades, after exposure. So are you going to continue to monitor these people then for their whole lives? How do you deal with a positive observation? It's not that straightforward.

DR. NELSON: Richard, did you have your hand up?

DR. GORMAN: With the lack of all previous evidence, or most previous evidence, pointing away from these agents as potentially carcinogenic or mutagenic or chromosomal affective, what motivated these researchers to look at this particular methodology to study this drug in this patient population?

DR. JACOBSON-KRAM: If you look at their paper, their motivation was, one, the large number of children on the drug, and the fact that it's increasing.

The couple of in vitro findings of increased chromosomal aberrations, the sister chromatid exchanges, and the one observation of the liver tumors in the mouse study.

DR. GORMAN: Given the long clinical history of these drugs in large populations of use, is there a particular target cancer we should be looking

at as a potential outcome of?

DR. JACOBSON-KRAM: The data that we have would not suggest a particular ? I mean aside from the El-Zein paper we wouldn?t be looking at all. So there is really no basis for looking at a particular kind of cancer.

DR. NELSON: Dennis, and then Michael.

DR. BIER: I just wanted to know a little more about the predictability issue. I mean is this a predictability issue when you have one hit, and an acute set of studies where you find this, and then the medication stops and then we're talking about cancer 20 years later? Or is this a repeated hits in people who take the medication over time?

What's the predictability? Is this from acute studies or is this from repeated studies?

DR. JACOBSON-KRAM: You mean --

DR. BIER: Well, if you have a positive chromatid exchanges, is that from a set of studies where we measured this once when a person started on the medication and gets cancer later? Or are you just talking about the frequency of those exchanges in people who have cancer?

DR. JACOBSON-KRAM: Oh, no, no, these endpoints are indicative of genetic changes that are

occurring as a result of some exposure which initiate the carcinogenic process that results in a tumor 20, 30, 40 years later.

DR. BIER: Are there any data on these kind of specific tests done in the population prospectively now for cancers later?

DR. JACOBSON-KRAM: Not that I'm aware of. That would be a difficult study to do. It would take 30, 40 years to do that. Now, for example, you can ? there are some chemicals which are known to be human carcinogens. We know that epidemiologically. We can then lo ok at populations who are exposed to those chemicals, and also controls. And what we find is, in fact, those people with the exposures have higher frequencies of these markers.

DR. NELSON: Michael.

DR. FANT: One of the problems that you mentioned with the paper was the way the data was presented. And that is a bit atypical with the way that data is usually presented, and it makes it hard to compare against historical information that's in the literature.

Were you able, when you went back and looked at the raw data, were you able to some extent to re-express their data in a way that is more

concordant with what exists in the literature. And if you were, how do the findings ? how do those ? the changes that you ? that they saw compare to ? I mean are the increases in the range of increases that you would have been associated with an increased risk of cancers? I mean where do they stack up in terms of where you see the risk really playing out?

DR. JACOBSON-KRAM: Well, we recalculated all their data while we were there, and expressed it in a more conventional way in all the relationships they'll hold.

So there is still an increase in frequency for every endpoint for every patient.

DR. FANT: And does that increase in the frequency fit in the range of the frequencies that you see associated with the increased risk in cancer?

DR. JACOBSON-KRAM: Yes. I would say if these data are reproducible, then they would be very concerning.

DR. NELSON: Just as a quick follow up, did you actually rescore their slides?

DR. JACOBSON-KRAM: No. That would be a huge undertaking.

DR. NELSON: Tom, and then Victor, Bob and Mary.

DR. NEWMAN: Yes, I think my question is similar to Dr. Fant's. It looked like maybe the increase was due to the rates being abnormally low at the beginning, rather than abnormally high at the end.

And that's just what I want to clarify is, were the rates of these sister chromatid exchanges and the chromosome problems after three months in the range that in the epidemiologic study were associated with more cancers?

And can you ? you said epidemiologic studies show that rates of these at baseline increase your subsequent cancer risk. Can you give any ? quantify how big an effect that is? Because what we're trying to figure out is whether this is at all plausible. If this is a huge effect, then would it translate into a very big effect on cancer that we would have noticed by now?

DR. JACOBSON-KRAM: You can't do that kind of quantitative comparison. Remember that the quality of the preparations, at least the ones that we looked at, were fairly marginal. So I wouldn't do an absolutely comparison between their frequencies and let's say the ones in the literature.

The thing that is concerning ? and I would say at the beginning that levels were abnormally low.

And that might be the result of the quality of the preparation. But what's concerning is the change. If their preparations were quality, stayed the same, then they're still seeing this increase. And that's what we're concerned about.

But we can't do this quantification of risk based on the numbers in the literature.

DR. NELSON: Victor.

DR. SANTANA: So kind of a follow up to that in that same theme. And this is more of a comment that's, as you all decide what studies to do in the future. One thing that struck me is, I have no notion of the relative effect that you're seeing comparing to known drugs that are known to cause DNA damage. And obviously it's very hard to do, because you can't give healthy children DNA-damaging drugs.

But in vitro assays could predict what the baseline is, and what the effect is, when you use a drug that is known to do these things.

And I think that is very important in contextual understanding of what this is really doing, either by class of drugs, or by known drugs that do these things.

The other commentary is, I still don't understand the chemical plausibility of why these

drugs are doing this, and maybe it's all speculative now. But why are these drugs doing this? What is really happening in terms of DNA damage?

And the corollary to that is that the balance of DNA damage to DNA repair. So we haven't really explored is there something with DNA repair that is really the problem here that is going to cause the epidemiological effect that hopefully you're going to be looking for in the future.

But these are just kind of general comments for you to think about. You don't necessarily have to respond to them.

DR. JACOBSON-KRAM: Well, the chromosomal aberrations actually are the result of lack of repair or misrepair. So we also assume that there is, whenever you see that, there is successful repair ongoing also.

So what you see is kind of what is left over after the cell has done its best to repair that damage.

In terms of the magnitude of responses, we certainly have data from both children and adults who were treated with antineoplastic drugs, many of which are also known to be mutagens and clastogens and carcinogens. And the magnitude of these increases are

not so different from what you would see in people being treated with antineoplastic drugs. So that's why we're concerned.

DR. SANTANA: What's the biochemical plausibility that these class of drugs do that?

DR. JACOBSON-KRAM: In fact --

DR. SANTANA: Because I can understand how platinum does it.

DR. JACOBSON-KRAM: Yeah, or cyclophosphamid, or adryamicin. But yeah, there is no obvious mechanism by which these drugs should be doing this, and there is nothing about them that would clue us into thinking that they could be DNA damaging.

DR. NELSON: Bob.

DR. WARD: My recollection is, in the '70s, LSD was associated with a lot of clastogenic changes that were subsequently found not to be associated with any carcinogenic abnormalities.

How many times does that lack of long-term correlation has that been identified?

DR. JACOBSON-KRAM: That was a different situation. That was not a comparable study. These were studies where people took LSD, exposed cells in vitro, and then looked for chromosomal aberrations. And many of those were just lousy studies, and so when

they did them right they found no clastogenic effect.

But I'm not aware of studies where they took people who took LSD and then looked at their peripheral blood lymphocytes.

DR. WARD: From the technical aspects that you describe, for those of us who are not in this arena, it does make us wonder if the technical problems with this study are what we're really measuring.

Are there also some epidemiologic analyses ? I was thinking of COG ? and I see Victor has stepped away ? but whether we have simply case control analyses that could be done in a six-month period, that look at children with cancer, and simply ask the question about long-term exposure. It seems to me that that is an obvious opportunity to obtain data more rapidly.

I know that people who are against the use of these drugs for treatment of children with hyperactivity think this is critical information, and I think we should be able to get it fairly rapidly.

DR. JACOBSON-KRAM: I would think so. You have to look at children that have been exposed 20, 30 years ago.

DR. WARD: Right, but I think that's

available.

DR. NELSON: Mary.

DR. GLODE: Just a quick methodology question, so I'm used to vaccine studies where you draw the blood, you freeze the serum acutely, you freeze the serum convalescent, you run them all the same day.

But so I just want to clarify, so that can't be done in this instance. You have to prepare the slides, whether you read them or not, within some period of time. And now three months go by, and now you do the same thing again. Is that correct, so there is that opportunity for different processing to have occurred; is that right?

DR. JACOBSON-KRAM: Right. In fact that was one of our questions, because the publication is not very clear on how they actually did it. So we investigated that when we went down to Texas.

The cells have to be cultured immediately, but they don't necessarily have to be made into slides right away. And once they're made into slides they don't have to be scored right away.

So what the investigators told us is that they made the slides ? they cultured them as they got them, but then made the slides and prepared the slides

and scored them at the end when all the samples had been collected.

DR. NELSON: With everyone's permission I'd like to move us on only to try and keep close to time.

If we have time before lunch with questions, we can come back to these issues in the context of adverse events. But to try and summarize what I heard, A, there is a cellular signal that's worrisome. B, there are epidemiological studies in other contexts that relate that signal to group differences in cancer rates. And third, we've not seen any of that as a safety signal in the epidemiologic studies in the use of methylphenidate.

Is that a fair summary?

DR. JACOBSON-KRAM: Yes.

DR. NELSON: And we don't know what's going on.

DR. MURPHY: But I would like to add, we are doing other things to try to better determine what's going on.

DR. NELSON: No, I understand. I'm just saying, where is our current understanding. Nothing to do with trying to figure it out going forward.

The next presentation is on the overview

and regulatory history of methylphenidate from Dr. Andreason.

DR. ANDREASON: Thank you very much.

I'd like to start off by first of all thanking Dr. Rappley for your presentation on clinical environment and what it's like to treat patients with ADHD. It was thorough and particularly touching because my daughter has ADHD, and has been treated, and was identified at age three with a non-attentive type.

And at that point in history, they didn't think that methylphenidate would treat anything except the hyperactive type, and she didn't start treatment with methylphenidate until she was eight. And we felt a little bit guilty as parents, and I as a psychiatrist, when we found that there was a marked difference, and she had gone five years without any pharmaceutical help.

That said, there are three different major classes of approved medical treatments for ADHD. The stimulants, including the methylphenidate and the amphetamine products, pemoline, and atomoxetine.

Methylphenidate has been with us since 1955 ? that's the year I was born ? and it has been labeled to treat attention deficit disorder under

several different titles. One title in the '60s was actually minimal brain dysfunction. That was coined by Paul Wender of the University of Utah. I actually had the opportunity to train under Dr. Wender at the University of Utah as a medical student, so I became intimately familiar with methylphenidate my third year, and then during my psychiatric residency when Dr. Wender was my mentor, and under several circumstances.

Just to add some historic perspective to how drugs are reviewed, and how this fits in with methylphenidate, it wasn't until 1962 that Congress amended the Food, Drug and Cosmetic Act to require that a drug demonstrate effectiveness prior to approval.

So Ritalin actually was approved based on safety data alone. Just as another kind of historical marker, it's 1962 that Francis Kelsey was recognized by President John Kennedy for her work with thalidomide, and her review of that and keeping it off the market in the United States, and its association with limb agenesis in foreign countries.

Since 1955 the methylphenidate products have undergone several formulation changes, but the drug substance itself has basically remained the same.

There has been several extended release varieties formulated, and this lists them. Concerta, that we're looking at today, is one of those.

Some formulation changes have also been made in the fact that there are solutions available in chewable tablets, and some drug substance changes have been made in that there are now stereo-specific versions of dexmethylphenidate available both in extended release forms and in shorter acting forms.

Now given that since 1955, or actually since 1962, drugs must be shown to be effective, the basis for approval for the treatment of attention deficit disorder is now made in patients who are diagnosed under the current criteria, and they have to show improvement in standardized clinical rating scales that measure attention in this population.

Most of these trials involve showing statistically significant improvement in classroom measures of attention and behavior in double-blinded randomized placebo control studies.

Some of the rating scales that are used are the Swanson, Kotkin, Agler, M-Flynn and Pelham scale, commonly referred to as the SKAMP. As a matter of fact I refer to it as the SKAMP so often that it's hard to actually say all the names.

And then there is the Conners scale, or the IOWA Conners scale, that is very common.

Another one that I haven't mentioned on that slide is the ADHD Rating Scale, or ADHD-RS scale.

One of the things that is striking about studies with amphetamines is that they are uniformly positive. In my time at the FDA, and I've been there 11 years and reviewing trials of stimulants, I have yet to see a failed trial of a stimulant.

Possibly the hardest thing for us to do as reviewers is to identify a minimum effective dose with stimulants, and to, say, perhaps cap what would be a maximum recommended dose.

Here is an example of just some of those rating scales. You'll notice that there is a roughly double effect in the mean response, and this is uniform across these studies.

Now Concerta specifically is a drug that is a methylphenidate product that is approved for a 12-hour duration of action. Now if there any pharmaceutical industry people in the audience, they know just how hard it is to get a duration of action claim from us. And it requires that multiple critical time points all be measured, and they all must show statistically significant separation in order to get

such a claim.

These claims for Concerta were based on using the SKAMP score ? the attention index of the SKAMP, and this is what it showed, over time, that this was ? in a laboratory classroom setting that at each time point, critical time point, there was a statistically significant separation from placebo.

Now, given that this is a laboratory classroom setting, this actually fits the criteria of an add-on study. This is a behavioral setting where these are people who are used to working with children with ADHD. It's a small classroom setting.

In other words, it's an ideal setting in which kids with ADHD can learn. So this is the drug effect over and above behavioral intervention.

So the conclusions, as we consider methylphenidate products generally, stimulants generally, and Concerta specifically, is that it's in a context where stimulants are a very reliable mainstay in the treatment of ADHD, and duration, given that duration of action claims are very difficult to achieve, and it still showed efficacy.

But the clinical benefit must always be weighed against adverse events. Methylphenidate products are stimulants, and they carry all the risks

that stimulant products ? or stimulants in general do.

Those risks are quite well known. Anyone who has read Goodman and Gilman knows what those are. In high enough doses a lot of the adverse events that we're going to be talking about today will be seen in almost anyone.

But given now the broad background of the prescribing population, even though these adverse events are well known in the psychiatric community, over my professional lifetime the prescribing practices have changed so drastically that we think that maybe we need to clarify and update the labeling so that people who have not been, say, trained by Dr. Wender, or trained in a psychiatry program specifically, can have a clearer idea of what those things are.

The labeling now contains terms that are inclusive and accurate from a term of art form. For example, there are terms in the labeling such as agitation or toxic psychosis, which to psychiatrists may be clear, but may not be clear to primary care physicians or pediatricians, and who have thought that it's probably time to perhaps flesh those out a bit more.

And that's the context in which we bring

these data, and labeling suggestions, to you.

Thank you.

DR. NELSON: Thank you.

With the committee's permission, what I'd like to suggest is, we hear the next talk on pharmacokinetics, and then entertain questions of the two together since they seem to be kind of a package. Okay.

On the pharmacokinetics is Dr. Kavanagh.

DR. KAVANAGH: Thank you.

I want to say, it's a pleasure to be here today and dealing with pediatrics. I'm sorry ? it's a pleasure to be here today and dealing with the pediatric committee.

I'm formally trained as a pediatric clinical pharmacologist. And I have quite a bit of adult training in psychopharmacology, clinical psychopharmacology.

I did not work on the Concerta approval or review. But I have been for the last four years working on methylphenidate within the FDA.

About two months ago I was asked by the neuropharmacology group, or told, we've heard about some reports of acute toxic psychosis in patients receiving Concerta as part of this review, this one-

year review required by Congress. And we're ? it's something of course we would expect, but the question that has been raised is, would it be any different with Concerta than any other product?

And I said, yes, that's an interesting question. I wouldn't mind looking into that. So my approach was basically to go back and pull all the ? or pull all the NDAs, as well as a number of generic drug applications.

And since this was not a formal question in these studies, these studies were not designed to test this or look at this, I basically used exploratory data analysis, you know, pulling the data, looking at it in different ways, plotting different graphs, and looking to see if I could see any patterns that would indicate to me, one way or the other, whether or not it would be any different between these products.

So in terms of my presentation, what I'd like to do is, first, give a very brief history of psychosis with methylphenidate itself. Then I want to give an overview of the similarities and differences between these different methylphenidate formulations. And then a little bit of talk about, well, how variable are they? And then finally, well, what kind

of exposures do we actually see with the doses that we would expect to be used clinically?

Well, as you've been told today from methylphenidate, Concerta, and other products, or as of 2000 when Concerta was approved, the maximum daily dose was 60 milligrams. And that's basically the way it was labeled for everybody regardless. Concerta, the maximum daily dose was 54 milligrams, and that's simply, you'll understand the reason for that in a few minutes. But it's basically very similar.

In 2003 when approval was given specifically for adolescents and that was the basis for the exclusivity and the basis for why we're here today, the labeling included doses up to 72 milligrams, but not to exceed two milligrams per kilogram per day.

Typically in terms of what you see clinically used, in the 1960s and '70s I have quotations in review articles as well as textbooks that the typical clinical doses are .25 to 1 milligram per kilogram per day.

And form what I'm seeing actually in these studies, for these different products, for what the kids are actually optimized to, the range is anywhere from about .3 to 2 milligrams per kilogram per day.

The average consistently is about .9 to 1 milligram per kilogram per day.

Now that is not to mean that the actual dosing has increased over the years. It may have, but on the other hand I'm very familiar with review articles and review work. And when someone writes reviews sometimes mistakes can be made. In fact in some recent reviews with methylphenidate, I've caught very obvious mistakes.

So to say that ? I don?t want to say that the dosage is actually any higher. I would actually have to go to the primary sources myself, and double check these numbers from textbooks and everything.

Idiosyncratic psychosis has been well known. It's clearly mentioned in Goodman and Gilman in the fifth edition from 1975, specifically in ADHD. And when I say idiosyncratic, I want to point o8ut that this does not mean rare. This means that basically we can't predict ahead of time who is going to get acute psychosis.

So we don't have a good handle on what the actual numbers are, but it's something, as Dr. Andreason said, if we give enough of this drug or any stimulant, we expect to see it.

And some people are just more sensitive,

and will have it at the typical clinical doses.

And even in Goodman and Gilman, which is a standard pharmacology texts that most medical students in the '70s probably used, it indicates basically that you see this idiosyncratically at typical doses in children.

So I want to, in addition, in Concerta, in the original NDA, there were several cases that were observed with the clinical doses that were used, and Dr. Mosholder who I see just walked in in his review indicated that he didn't feel that the incidence of the Concerta was any higher than other methylphenidate products. And he is a pediatric psychiatrist.

In addition since then other pediatric psychiatrists within the FDA have reviewed annual reports, and also seen annual reports mentioning acute psychosis and so on. And typically again it's well ? it doesn't seem to be any higher than what we would expect. This is normal reporting.

So it's not that this is something new, or that this is something at a higher incidence. But in fact also, as I said, in the Metadate CD in the NDA, several cases were observed.

So it may not be appreciated how frequently it can occur, and we don't know for example

how frequently it actually occurs. But that's part of where we've been going the last couple of years in making the labeling clearer. And you look at the progression of the labeling from when Concerta was approved to some of the newer once-daily methylphenidate products, and we have actually been trying to make it a little bit clearer in terms of the format.

So I think we're in a progression of trying to communicate better.

Now let's look at the various methylphenidate formulations. Oh, I'm sorry, is there any way we can ? I guess it's okay on the screen.

In general we have two broad classifications: immediate release methylphenidate products; and then modified release, which are the once-daily products.

Under the immediate release you have Ritalin tablets, of course, and then the d-isomer Focalin. And then you also have the solution and chewable tablets.

And the reason I ? and one of the things you have to realize is, methylphenidate is very, very soluble. A tablet, once you swallow it, probably turns into a solution in your stomach within five to

10 minutes. It's incredible.

It's a very well absorbed drug, and so basically, if you take a tablet, it's just about like taking a solution.

Now, the drug like many drugs is not absorbed in the stomach. The stomach is not designed to absorb things. So basically what you have to do is wait 20 minutes to a half hour, somewhere in there, before the stomach starts squirting things out into the small intestine.

So you wind up having about a 20 to 30 minute ? and typically since we talk our first measurements at a half hour, we wind up having a lag time of about half an hour before you start seeing any drug in the body. And so you see that up here.

Methylphenidate and these solutions are then well absorbed. And you wind up getting a peak at about an hour and a half.

Oh, I'm sorry, thank you. All right.

So basically you have a ? this is a 24-hour scale, and for each of these there are 24-hour scales. Now I don't want you to pay attention really to the scale here, because these are different scales on the side, and I simply did it to make the time axis similar. And to maximize the peak, to make these look

? be more obvious.

So basically they're all immediate release that basically behave like solutions, have a lag time of about a half hour, peak at about an hour and a half, and then decline anywhere from two to 3-1/2 hour half life.

Probably as we start getting down to 6-year-olds, it starts going toward two hours and such. I have very little data on 6-year-olds, but that seems to be about what I'm seeing.

Ritalin SR is a classic extended release formulation. In other words, it's a slowly dissolving tablet. And so what you have instead is, again, a half hour lag time, and then it slowly releases and with a peak about five hours out on average. This although it's a sharp peak, that's just variations in the assay in the individual normal sampling. But what you expect is kind of a rounded top, okay?

And so absorption probably continues out to about this point, and then it declines. And this is first order release. In other words it's a constant percentage. So for example just to use round numbers, say 100 milligrams, in the first hour 20 percent of the dose is released, at the end of one hour you still have 80 milligrams in the intestine.

The second hour another 20 percent is released, so that would be 16 milligrams. So in the second hour 16 milligrams would be absorbed, and that would continue to increase the percent every hour that's being released from this would continue.

Concerta on the other hand is a combination, the extended release portion is zero order. And then over that release mechanism is this layer, and it's about four milligrams out of the 18 milligram tablet, where it's coated with an immediate release layer.

So that immediate release layer also behaves like a solution. You get this half hour lag, 1-1/2 hour initial Tmax right here, similar to immediate release products.

Now when I say zero order, what I mean is that instead of a constant percent you have a constant amount. So of the remaining, let's say, 14 milligrams out of an 18 milligram tablet ? and I don't remember the numbers offhand ? but let's say it would be three or two milligrams every single hour would be released. And it does not vary.

And the mechanism is such that it's really unaffected by the contents of the stomach, whether it's acidic or whether it's basic, and the pH and the

osmotic contents of the intestine, it's really not affected that much.

So it's a very consistent mechanism. So what you wind up having is the second peak ? you have winding up a plateau. It actually does decrease, but it kind of ? it's so tiny that it's really kind of a plateau for about three hours, on average, and then it kind of goes up to a peak at about six, 6-1/2, seven hours, and then it declines.

With Metadate CD, this is a combination. It's a bunch of tiny little beads that are in a capsule, and it's kind of like Contac where 30 percent of the beads are immediate release, and the other 70 percent of the beads are basically beads with a classic extended release slow dissolving formulation.

So what you have is the initial immediate release portion. And you would say, well, it's only 30 percent and 70 percent, so the first peak can't be as high as the second peak. But the thing is, because it's a slow dissolving, the dissolution of the slow dissolving begins very rapidly like this, or begins ? it just takes longer.

So it's basically kind of a superimposition of this right here on top of the slow dissolving portion. So it winds up the two peaks

being similar with not too much of a trough in between, an inter-peak minimum.

Ritalin LA is also a combination of immediate release beads ? 50 percent ? along with a modified release bead.

But these modified release beads are different than this. These modified release beads are such that they're pH dependent. So they don't start dissolving until they've been in an environment of a pH 6.5, in that range, for several hours. So they have to be in the small intestine for at least several hours before they start dissolving.

So what you wind up is basically two ? you know, the first peak and then the second peak, and with a greater peak-trough fluctuation than with the Metadate CD.

And this is designed to really mimic two individual doses clinically, which is what we use, without having to give two separate doses, a second dose at lunch.

Now, what about ? what about concentrations or exposures between these? And I'm focusing mainly on the maximum concentration because the maximum concentration is what we would expect to be most likely to be related to acute psychosis, as

well as probably some of these other side effects, as well as to some extent the rate of absorption, okay, to some degree.

And so that's why I'm looking at Cmax. And what I did is, I took ? and I looked at, well, here's three doses of immediate release formulation, given four hours apart. And if you looked after the second dose, it would kind of decline like this. The third dose, basically goes a little bit higher you would expect. But basically about the same, and then declines.

And I took the average concentration of two 10 milligram doses at the second peak, so the second 10 milligram dose as my reference point, and used that.

Now if you look at Ritalin SR, and also look at the same dose, 20 milligrams, because it's absorbed slower, more elimination is going on here, and the average peak concentration as you would expect is just a little bit lower. So it's about 90 percent.

For Metadate CD it's also a little bit lower, about 90 percent for the second peak. And even though this graph looks a little different, this is because I took it from an individual. And individuals do not always fall exactly on the mean.

This is mean data, or this is for Concerta, and the mean peak is about, again, about 90 percent. But Concerta, remember, is like 54 milligrams to 60 milligrams, the maximum dose. So if you would actually have given a dose of, say, 60 milligrams, you would expect the same peaks of 60 milligrams of, you know, of other methylphenidate products, immediate release I should say.

And Ritalin LA, the second peak is about ? first peak is about 70 percent, and the second peak is about 80 percent of this reference peak. And these are averages.

So as expected, on average all of these are basically in the same ballpark, with the longer lasting drugs as we would expect, because of the slower absorption and everything. When you normalize for dose and give everybody the same dose, they basically produce at about the same peak concentrations.

So what about the variability from one subject to another and everything else? Different people receive different doses, and when you look across these various studies and everything, we see ? I see at least, looking at these NDAs about a fourfold range in peak concentrations.

On average, though, and when you normalize it to milligram per kilogram dose, basically it's the same. It's methylphenidate, it's methylphenidate. So the average peak concentrations when you normalize it to the same milligram per kilogram dose, it's basically about the same as I showed you in the previous graph, regardless of product.

Inter-subject variation: we're talking about averages and even differences in variability in large groups. But we know that each individual doesn't absorb the drug the same way every single day. There are different things going on with your GI tract. You have diarrhea one day, you have constipation another, you eat something different. So there is individual variability.

And to look at this, what I looked at in this study, I normalized Ritalin to a dose of 10 milligrams given twice daily, and Concerta, 18 milligrams. So basically this is comparing a single dose of Concerta, 18 milligrams, to the second dose of Ritalin, 10 milligram dose of the day, of Ritalin tablets.

And as I said before the average was about 90 percent, but the range here is about ? that we actually see is about 40 percent lower to about 30

percent higher, and probably a little ? probably actually wider than that. This is adults, and it's a small number of subjects.

But basically you have on average what an individual could be, one day could be lower, and another day could be higher, or you know ? but this is two different products.

Looking however at the different products in the same individuals, and this is a study with 36 individuals, and this is out of the 36 individuals this is the subject with the lowest concentrations with Ritalin tablets.

And you also see that this person also has very low concentrations with Concerta. This is the average for all 36 subjects for the Ritalin, for the peak concentration, the red line.

Also has very low concentrations with Concerta, and also has very low concentrations for Ritalin SR. So basically if you have low concentrations for one, you're probably going to have low concentrations for another. Out of the 36 this is the individual who has the highest Ritalin concentration, also has high Concerta and high Ritalin SR concentrations.

So if you have high ? and this is just an

individual who just happens to match up with about the average data. And so basically what's happening in terms of your overall exposure to one happens with your overall exposure to the other products.

One of the things I want to point out, what we would expect is typically maybe the third dose, your "S" should be at about steady ? you should be steady state by the second dose, or the third dose. So these should be basically similar with maybe the third concentration a little bit higher.

But you see it just happens to be that in these particular subjects the second peak is a little higher. Other subjects, the third peak is quite a bit higher. But that just kind of shows to you the intraindividual variability that actually occurs. You know we can't always talk about mean data and everything else. We don't actually know in practice what's happening from dose to dose.

Now looking at the repeat variability with Concerta from one dose to another dose a week later, in the same individuals, and you would expect on average that they would be the same exposures, because by the next day the drug is totally out of your body.

And the average is, you know, let's see, this is the immediate release of the third dose of the

day to the second dose of the day, it's about 86 percent, with a range of about 40 percent to about 120 percent, the third dose of the day.

So that shows you the variability of the immediate release, even though you would expect that they all behave like a solution where the formulation shouldn't matter.

So that kind of indicates more physiological variability. And Concerta, you'd be looking at one dose from one day to another dose a week later, you'd see again anywhere from a week later, the concentrations are half to almost twofold higher compared to the baseline.

So basically ballpark it kind of looks like from day to day the peak concentrations can probably vary twofold from one dose to another, in the same individual.

What about food? This is taken in the morning. It's taken with food. Well, what we typically do is, we do look at the effects of food. And I'm going to show you the effects of food.

One of the things I want to point out is that when we talk about food effects, we want to see the worst possible scenario. So we give them lumberjack meals. And these are in adults. But

basically we give them sausages, we give them pancakes, we give them eggs, we give them hash browns, we really load them up with calories and everything else to see the worst possible scenario. If under worst possible scenario you don't see anything, well, obviously, with a typical breakfast, you're not going to see anything either.

So I don't want people to get the wrong idea.

Well, this is three different formulations: Ritalin LA; Metadate CD; and Concerta. And the top graph, these are time metrics, the lag time, the time to the first peak, the time to the second peak, and one that a trough in between occurs.

And the top set of panels in each case is under fasted conditions, and the lower one is under fed conditions. And basically what you see with all of them for the immediate release component is, under fasted conditions a lag time of about half an hour, and as you go to fed conditions it increases somewhat, so some individuals or more individuals wind up getting no drug absorbed until an hour, sometimes an hour and a half out.

And that also kind of then also delays the first peak, so compared to an average Tmax, time to

first peak of about an hour and a half, it's slightly later, maybe about 2-1/2 hours. And that's consistent for the immediate release portion for all of them.

Because the inter-peak minimum is really dependent ? depends upon the first peak and the second peak, I'm going to skip this and go right to the second peak.

And what we see here with Ritalin LA is, you know, if we come down the peak is probably about looks like about five, six hours out, something like that, and then with food it really spreads out quite a bit.

And my guess is because this is pH dependent. As it gets mixed up in all that food, the acid ? or the fluids in the gut can't get to these formulations. And it depends on where it's mixed and where it is in that food that's traveling through your gut.

So you wind up having a lot of variability into the time of the second peak.

For Metadate, we see again a widening, but it's hard to tell, and really what's happening, if you look at the total numbers here, as compared to here, as well as total numbers at the beginning, there is really not that many individuals who we're seeing the

second peak in. And basically what's happening is, the concentration curve is flattening out, and we wind up in a lot of individuals only kind of getting a single peak. It just kind of all meshes together.

With Concerta the time to the first peak is about 6-1/2 hours. You know you have some individuals up like eight hours. Most of them are at six hours. With food it does get delayed, but it's still, since it's a single large tablet, it's more consistent, and because of the mechanism and it's being pumped out. So you wind up, you do get a delay.

Well, what is the effect of this on concentrations? And I know what happens with drugs, and I can predict what's going to happen to the peak concentrations, but I just want to show you.

Here's Concerta, and I just took four individuals right from the mill, they're numbered one through 36, I just grabbed four right from the middle. And if you look at ? and these are fasted, and the same individuals under fed conditions, side by side. And you basically look. And you can kind of see same to similar or same to slightly different times to the peak concentrations, and in terms of the actual peak concentrations themselves, in this case it didn't change, and in the other ones, it changed maybe at

most 20 ? 25 percent in some of these individuals.

Looking overall what we see is on average that this peak here with Concerta increased on average about 15 percent, which is really you know not that much. The first peak, however, increased quite a bit, but the thing is, oh, looking at it this way, that looks horrible.

But you got to remember that that first peak is really a shoulder on this portion, so it's already like at baseline less than half the actual overall peak. And so basically what you're doing is simply shifting this and causing the shoulder to ride up and actually kind of occur up here on the side.

So percentage wise it's high, but in terms of toxicity or whatever, it doesn't even get as high as the second peak. And that actually, that 15 percent rise in the second peak on average is because some of this is being shoved underneath this portion here and kind of lifts it up a little bit.

For Ritalin LA this first, unfortunately it's a little hard to see, but this concentration profile is under fasted conditions. The second one is under fed conditions, and you see the first peak is a little bit higher, and with a delay here. The second peak is also delayed, but it's lower, and you have

less peak-trough fluctuation under fed conditions compared to fasted conditions.

And this is a decrease of about 20 percent. So in theory, if you're looking at overall averages, and this increases about 15 percent, and this one decreases about 20 percent, if you go from taking Ritalin LA with a super, super heavy meal every single morning to taking Concerta at about the same approximate dose, it's basically like going up one dose level.

So that typically is not ? it probably is not such a big deal. People go up one dose level all the time. But it is, in some individuals might cause a problem, but in general, not something to really worry about. And that's what this slide is suggesting is what happens when you change.

Well, what kind of exposures do we see with the typical doses that are used clinically? And what I want to do here, I wish I could step away from it.

What I want to do here ? I wish I could step away from the microphone ? typically a starting dose is about point three milligrams per kilogram a day. And as I look across the various MDAs and see what doses the children have actually been titrated

to, and what they come in on, to what is an optimal dose, and this happens to be for Concerta but this also holds for the other drugs too ? thank you ? the typical dose range is about .6 to 1.5 milligrams per kilogram per day with an average dose that the children will optimize to, .9 in one study, 1 in another study, and so on.

And some kids are receiving 1.8 in this study. In other studies we have some kids receiving as much as 2. But the vast majority ? and some kids are actually receiving .3. The vast majority of kids are in the .6 to 1.5 and some, a smaller percentage going up to 1.8, and a smaller percentage to .2.

Now there is a very close relationship between dose and peak concentration with these products. And this is specifically for Concerta, but as I said, Concerta, there's really a 10 percent difference in the various peaks for the different products. So this is going to hold for all the products.

And we see for the dose, this is a linear relationship. Now the blue line is adolescence, and the red line is six to 12 year olds. In this case it's seven to 12 year olds. And even though ? and this is lower, so if anything, the younger kids are

going to have a little bit lower peak concentrations than adolescents, but only by about 10 percent on average. This really isn't much different here, at least down to about seven, six years old, which is the labeled dose range.

So if you look at the dose range of .6 to about 1.5, you would expect concentrations to be in about the seven to 20 range as you go up, to 1.8 and even 2.0, probably going up to the 25 or 30 range, 20 to 30 range in some kids. And now looking at the data points, these are actual peak concentrations for their optimized doses, and that's what you actually see. Most kids, their peak concentrations fall in this range, with some in the 20 to 30 range.

And we also see this with the SKAMP testing, and I can basically relate concentrations and peak concentrations to about the degree of improvement on the SKAMP scales.

I don't want to overemphasize that, because it's very, very complex in terms of details. But there does seem to be kind of a ballpark range in terms of what is an optimal dose. They're having clear effects, they'd doing quite a bit better, but they're not ? but overall most kids are not having excessive toxicity.

That does not mean that someone who gets a dose down here cannot have undesirable toxicity, and they can't tolerate the drug. That's just normal variability, and we would expect it. Some kids ? here's a kid who happened ? a seven year old who got a 54 milligram dose, you can see very, very high concentrations.

But this was basically, the kid was able to tolerate it. So there is ? intra ? there is individual variability in how kids are able to tolerate side effects and so on.

Now this is simply to show you with a different product. This is a 40 milligram dose of methylphenidate in adults. And typically study after study, NDA after NDA, adult weights average are about 75 kilograms.

So a 40 milligram dose in adults is about .25 milligrams per kilogram. This is going to be about .5, this would be about .75 or whatever. And these are just random blood samples taken from individuals who are on these drugs over the course of a day. And this is a long acting product, a different product.

And you can see that with this low dose, kind of a starting dose, in a lot of individuals,

you're down in the single digits with kind of the more typical dosing you're in that 10 to 20 with some, if you look at averages, this is probably about 12, this is high teens, you're going up into the 20 and 30 range. And that is typically what I see when I look across products, consistently again and again and again.

And I don't have ? with this kind of data you can't really say, well, this is the peak in this individual or whatever. But I can say that this is ballpark, kind of what I'm seeing.

So if you look at concerted dosing, and as I said before, it's not labeled on a milligram per kilogram basis, even though if you look at the history from even initially study ? literature articles from 1963, '64, and it talks about starting at .3 milligrams per kilogram per day and increasing the dose.

Well, if you look at 54 milligrams, and you look at an average weight kid, and I'm talking over the age of six to 18, so the children's and adolescents', and we look at a 54 milligram dose, and if I pick 1.5 as basically my typical upper limit, and I pick 1.8, some as 2, as you go down at about 10 years of age, a 54 milligram dose on average, average

weights, you're beginning to go above that 1.5 milligrams per kilogram per day.

And so probably as you go lower you would expect that this, and as you go in a lower range more kids, the six year old, more kids are going to be like that.

And when I actually look at what the doses are that clinicians are titrating their kids to, that's exactly what I see, in terms of ignoring the milligram per kilogram dosing, but that's basically about what I see in terms of the doses that are by age.

So this is taking an average weight kid. Question is, not everybody is average weight. So anyway, so looking at ? so what I did is take what happens right at about their birthday, and if they happen to be extremely low weight.

So these are basically what I would expect for kids on average who are like maybe a week or two shy of their birthday for that age, and are also at the lowest fifth percentile. And you see that the 54 milligrams on a weight ? milligram per kilogram basis, it's quite a bit higher. And then the same for these other doses.

Taking those plots that I showed you

before in terms of milligram per kilogram dose, and looking at what the concentrations could be, you would say, well, you gave a 54 milligram dose to a super lightweight six year old, on average you might expect peak concentrations of about 40. And if you figure in the twofold variability, well, so ? so anyway.

I'm sorry.

Basically what we see ? and this is actually a misnomer, low variability. What I mean by that is really, it's really more consistent, and you consistently see about a fourfold variation.

And that's pretty typical for many drugs. Some drugs that are what we call highly variable might be 10 or 20 fold. So this is kind of normal variability. It's really not low variability.

But the intra and inter-subject variability, there is about fourfold inter-subject, twofold inter-subject variability. And when ? but when you dose normalizes, that will take care of on average, that corrects some averages .

Looking at all this data together, and looking at the patterns, and looking at how these drugs are made, and how they release things, and what you do to them in the test tube, and whether or not they release it, there is really no indication that

the risk of toxic psychosis is any greater or any different than Concerta compared to any of these other formulations.

But again I want to say that these are serious risks ? or serious adverse events. I mean people ? they are very scary. We know they're managed. You know, you stop the drug, they go away. You lower the dose. If you just raised the dose and a kid gets it, or an individual gets it, it goes away. And they go away very quickly.

Cardiovascular risks are also very serious and are something to be concerned about, but we've known about this. And I've showed you about knowing about it from the '60s. Well, this works the same, it has the same mechanism or very similar mechanism to cocaine.

Cocaine we know from classic use probably people knew about it, and it improves attention. But that's clear, it does improve attention. So the thing is, is the risk any different? The risk is about what we expect; it's just more, they've been around, we know about them, but now there is a lot more people who are asking their physicians and everyone else for them.

We've been moving, if you've looked at the

label in the last couple of years, to make the risks more obvious. Not that the risks are any different than we've thought in the past; we're just moving in the direction of clarifying and communicating what the risks are.

Thank you.

DR. NELSON: Thank you. So if I could just summarize what I heard in the last two presentations, and then see if there are questions before our break.

And Bob, first, is that the methylphenidates are uniformly shown to be effective, and that there is predictable changes in pharmacokinetics and a predictable dose response relationship that may be affected more by formulation, but that appeared to be able to be dealt with as a class as opposed to as a specific drug.

So that's at least my take home messages from those two presentations.

Bob.

DR. WARD: Various drugs' effects correlate with AUC, Cmin, Cmax. Could Dr. Andreason and Dr. Rappley and you, your modeling is elegant but it's all based on Cmax --

DR. KAVANAGH: Yes.

DR. WARD: -- it appears, as opposed to AUC, which I'm used to thinking of for exposure. But do we have some correlation between these pharmacokinetic parameters in both effect and adverse effects? That's Cmax, Cmin or AUC, do we know which is more important?

DR. NELSON: Just to point out for those non-pharmacologists, AUC is area under the curve.

DR. ANDREASON: Personally I don't. Ron, do you have any information on that?

DR. KAVANAGH: Yes. Different types of effect you would expect to correlate better with one versus another. And it depends upon how the drug is distributed, as well as what is the underlying pharmacologic mechanism of the drug.

So AUC is totally ? is basically a measure of total exposure to the drug. And as you heard the AUC total exposures are very similar across these drugs. Basically they're well absorbed, and you know, a lot of it is metabolized by esterases, and that's what you see the very ability, the esterases are in plasma, plasma varies by body weight. You correct by body weight. The AUCs do not vary. It's the time course, and how ? what happens with the AUC that varies.

And so really ? and also, it's also the mechanism of these drugs. The mechanism of the drug is that it blocks dopamine being reuptake ? taken back up, and that occurs very quickly, microseconds.

And so basically you would expect a tight correlation to what is the actual concentration at the neuron to what's happening to dopamine and everything else.

Now there are other effects downstream and whatever. But so you would expect for at least acute psychosis, and also effects on the cardiac system, which is right in the bloodstream where you're directly acting on the nerves, you know, and there is not going to be a lag time or anything, that it would be more related to what is the actual concentration, rather than total AUC.

And I alluded to this that rates of absorption, how quickly you go to Cmax, might have ? might be expected to be something to look at. Looking at it in the data and correcting for a lot of underlying confounding variables is not an easy task.

DR. WARD: Your last statement I think is pivotal, and my concern is that you have made some hypotheses about the etiology and causation for the adverse effects correlating the Cmax or time to Cmax,

but I don't know that we have data that support that as opposed to it being still hypothesis.

Could you address that?

DR. KAVANAGH: Well, I mean, I think if you look at things ? this crosses the blood-brain barrier. I mean when you look at the SKAMP scores compared to the concentrations, and follow the concentrations in an individual, and you look at the SKAMP scores, and the effects on the brain, and you use very sensitive psychometric testing, and eliminate the variability of behavioral modifications and everything else, we wind up seeing a very close correlation overall between the time course of the concentrations, and what happens with how the drugs affect you.

Now just ? but in terms of ADHD, it may not necessarily be a low amount of dopamine in the brain. It could be a low sensitivity. So an individual who might have a low sensitivity to it, to dopamine, and you increase it ? and these are nonspecific. It's going to increase dopamine in other areas of the brain. So they could have ? so you could wind up causing psychosis because of an effect on another part of the brain at a low dose in an individual.

But again, you're probably again looking at peak concentrations, time course, and if you go up there are other things like looking at cocaine, methamphetamine, things like that, the way it's abused, looking at time course, what we would expect.

So I think looking at the literature overall, I think I have a very strong case.

DR. WARD: I disagree. I think the SKAMP scores that were shown, if we followed your reasoning, then we should see the SKAMP scores get dramatically better and then fall off during the day as these concentrations fall with Concerta. But the SKAMP scores look like they were fairly consistent throughout the day with improvement, compared to placebo.

See what I mean? So I'm not sure that we understand fully that mechanism, both for effect and adverse effect.

DR. ANDREASON: I can actually answer, or address, that one. Over that 12-hour period, the blood levels actually do stay in that range, and if the blood levels drop down, the effectiveness drops off.

DR. NELSON: Let me go to Marsha, and I do intend to take our break soon. So I'd like to give

Marsha the last question rather than speculating a lot about hypotheses that surround the data.

DR. RAPPLEY: I do think there are some interesting things that we you learn more, we understand what we don't know basically.

A lot of patients report changes in their mood, their irritability. People observe this as medications are changing, either kicking in or wearing off. And that's probably an area of study for some of these adverse effects that are related to mood and irritability.

The other thing is that when we measure behavior, when we measure tension and mood, those are gross measures, and don't have a precision of nanograms per mL, or the same kind of precision we get with imaging studies, which might also be helpful to understanding the relationship between the dose and what happens at the level of the neurotransmitter, and then what happens to behavior.

That's hard to do because you can't get the behavior very easily under an imaging machine. But I think that we've long held that concentration was not very closely tied to outcome, and that's why we don't measure levels clinically.

And the fourfold variation that you're

seeing in individuals are not necessarily seeing fourfold variations, at least that we can measure with our gross measurements, in terms of behavior and attention clinically.

I also am a little puzzled, and it's not just your data, we see this consistently over and over again, the younger children metabolize this faster, but yet they're more sensitive to the higher doses. And so is it the timeframe that they're metabolizing it faster, it's out of their system, but yet their initial dose is hitting them at a higher concentration.

DR. KAVANAGH: It would be ? with a faster metabolism, or faster elimination I should say, you would actually have a lower peak that occurs earlier. You know, I mean we're ? I'm dealing with data down to six years old, and most of these patients in these studies are in the 10 to 12 year old range. I mean it's hard to enroll a kid, have a parent say, we want your kid to go into a drug study with a drug that's never been ? at a six year old.

DR. RAPPLEY: What we know clinically though supports your limited data, that the younger children may need five doses, four or five doses a day. And that's what your limited data shows also.

But yet they're more sensitive to it.

DR. KAVANAGH: Well, I'm not necessarily sure about the sensitivity ? I mean it gets into a lot of things in terms of behavior and development and those are compounding variables.

So adults, I mean as you grow up you wind up developing compensatory mechanisms and control things. And we talked about the kids who at the younger age, preschool, I got a 5-year-old, I got a 2-year-old, you expect their behavior to be different, and their control.

DR. RAPPLEY: But they do have more appetite suppression, more headaches, more stomach aches. And I agree, it is a developmental phenomena, behavior issues. But there is also that sensitivity ? they just have more severe and more frequent side effects. And the studies are pretty consistent that show that.

DR. KAVANAGH: Right, but the thing is, have you controlled for the milligram per kilogram dose. I mean physicians, if you have 54 milligrams or 60 milligrams available, that's what people are going to be saying, well, that's the maximum dose.

DR. RAPPLEY: Limited studies on the 6-year-olds aren't using doses that high. In the

preschool studies they're not using 54 milligrams per dose.

DR. KAVANAGH: But even so what is the actual milligram per kilogram dose? You know, if a lot of six and seven year olds, the average dose is 1.2, and in the older kids the average dose is .6, I just recently in the last couple of weeks pulled all this data together across studies, and even then it's just beginning exploratory analysis.

So these are good questions, but I don't have answers to. And may be differences, may not be. We haven't looked at. Nobody has looked at it.

DR. NELSON: On that note, I think it's time for our break. I suspect once we have the adverse events on the table there will be a lot of discussion about trying to see if they correlate with drug, et cetera, et cetera. So I anticipate that our question and answer after the adverse events will come back to this.

So thank you for your presentations, and we will restart hopefully at quarter of, so the break is not quite 15 minutes.

Thanks.

(Whereupon the aforementioned proceeding went off the record at 10:34 a.m. to return on the

record at 10:48 a.m.)

DR. NELSON: So we're now going to move to the adverse event review for Concerta and other methylphenidates that Dr McCune will be presenting. And then after that we will have an opportunity for questions and discussions.

DR. McCUNE: Thank you. Good morning, Dr. Nelson, ladies and gentlemen of the committee and guests.

My name is Susan McCune. I'm a medical officer in the Division of Pediatric Drug Development here at the FDA, and like a couple of members of the committee, I'm a neonatologist.

In terms of an overview I'm going to first give you some background information which is going to actually review some of the information that has already been discussed this morning, maybe in a slightly different light, to put it in a slightly different context.

I'm then going to give you the information about the clinical trials for the initial approval for Concerta, and that was one in six to 12 year age patients.

I'm then going to discuss the clinical trial for exclusivity that was done in adolescents.

I'm going to give you methylphenidate used information for the one-year post-exclusivity period and the few years prior to that.

And then I'm going to focus on the adverse event reports from Concerta, and the one-year post-exclusivity period.

In terms of background drug information, Concerta or methylphenidate hydrochloride extended-release tablets are produced by ALZA Corporation, and are a central nervous system stimulant.

The indication for the use of this drug is the treatment of attention deficit hyperactivity disorder, or ADHD.

The original market approval was August 1st, 2000, and pediatric exclusivity was granted on December 4th, 2003.

In terms of the mechanism of action, the therapeutic action, the definitive therapeutic action of Concerta is unknown, but methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the external space.

Now this is to give you an idea of the dosage forms of Concerta. This is 18 milligrams to 54 milligrams, and as you've heard this morning by Dr.

Kavanagh, the release mechanism is one of an OROS trilayer where you have an outside drug overcoat. You then have a first drug compartment here. You have a second drug compartment here. And a push compartment here.

And as you can see there's an exit for the drug at the top of the capsule, and what happens is, the first drug dosage is released, and then throughout the day this push membrane pushes up the second dose to then be released.

I'm also going to talk just very briefly about what's in the literature. You've heard extensively about this from Dr. Rappley this morning. This is from the Clinical Practice Guidelines, just to put into context the drugs that we've been talking about this morning.

There are stimulants as Dr. Rappley pointed out as first-line treatment. There are nonstimulants, and there are antidepressants, which are second line treatment. And the antidepressants are not FDA approved for ADHD treatment.

And in terms of the group of drugs that we're talking about, in the methylphenidate category there are short-acting drugs, intermediate-acting drugs, and long acting. And we're talking today about

Concerta, which is one of the long acting drugs.

There are also amphetamines, that can either be short acting, intermediate acting, or long acting.

There's pemoline. Cylert was discontinued by Abbott, but there are generically available forms of pemoline.

In terms of nonstimulants, atomoxetine was discussed here this morning, but we're not going to discuss here today. And in terms of antidepressants, the tricyclic antidepressants and buproprion.

Okay. In staying with the literature I just wanted to use one of the tables from Dr. Rappley's 2005 New England Journal article just to show you that for the drug category of methylphenidate the side effects and the contraindications that are listed in the literature reflect what is on the label.

Okay, now let's talk about the initial studies for Concerta approval. The original market approval was in August of 2000. This was based on three double-blind active and placebo-controlled studies in 416 patients who were six to 12 years of age.

They compared Concerta once daily, either 18, 36 or 54 milligrams, to methylphenidate given

three times daily over 12 hours, 15, 30 or 45 milligrams as a total daily dose, and placebo.

Studies one and two were single center, three week crossover studies. Study three was a multi-center, four-week parallel-group comparison.

The primary comparison of interest in all these trials was Concerta versus placebo. And I'm going to show you once again the slide that Dr. Andreason showed this morning in terms of the efficacy results for the clinical trials.

This is if you look, these are study one, study two, and study three. This is inattention or overactivity. And then dark is Concerta and light is placebo, and this is the mean for community school teacher IOWA Conners inactivity-overactivity scores.

So if you're less inattentive you actually are doing better. So Concerta in all three of these studies showed statistically significant improvement in inattention and overactivity.

Okay, in terms of the adverse events from the clinical trials for the initial studies, in study three, discontinuation of treatment due to sadness or an increase in tics. And that increase in tics was actually a placebo patient.

In the two open label long-term safety

trials of 24 months and nine months, the overall rate of discontinuation was 6.7 percent. Insomnia in 1.5 percent of patients, twitching in one percent; nervousness, .7 percent; emotional lability, .7 percent; abdominal pain, .7 percent; and anorexia, .7 percent.

And these are ? this is table four from the label, and this describes the incidence of treatment emergent events in the four-week placebo controlled clinical trial. Headache, abdominal pain, vomiting, anorexia, dizziness, insomnia, upper respiratory infection, increased cough, pharyngitis and sinusitis are listed as increased events in the Concerta patients.

Okay, based on the initial studies for Concerta, the approved labeling included a number of sections of the label. And I want to spend a little bit of time on the safety sections of the label, because there is a lot of information on a lot of different places on the label, and I think that is something that is going to come back around as a discussion point.

In the contraindication section, agitation is contraindicated. Marked anxiety, tension and agitation are contraindications to drug use, since the

drug may aggravate these symptoms.

Hypersensitivity to methylphenidate is a contraindication.

Glaucoma is a contraindication. Tics or a family history or diagnosis of Tourette's is a contraindication. And patients on MAO inhibitors.

In terms of warnings, there are warnings about long-term suppression of growth. There are warnings that methylphenidate may exacerbate behavior disturbance and thought disorder in psychotic patients. There are warnings about seizures, about the potential for gastrointestinal obstruction, about hypertension and other cardiovascular conditions, about visual disturbance, and about use in children under six years of age.

There is also a boxed warning in the warning section about drug dependence describing tolerance, psychological dependence, psychotic episodes, and severe depression.

There is another section in the safety part of the label for methylphenidate, and this is titled, adverse events with other methylphenidate products. And I'll refer to that as I go along, just by that title, as adverse events with other methylphenidate products, but just so you know that

I'm talking about this particular place in the label.

And I just wanted to point out a couple of adverse events. Blood pressure and pulse changes, both up and down, tachychardia, angina, cardiac arrhythmia, Tourette's, toxic psychosis, cerebral arteritis and/or occlusion, and transient depressed mood.

There is also an overdose section in the label, and I wanted to point out a couple of things in the overdose section as well, including agitation, convulsions, may be followed by coma; hallucinations; and cardiac arrhythmias.

Okay, now I'm going to tell you about the exclusivity study that was done for Concerta. Exclusivity was granted in December of 2003, and this was based on a clinical trial that was done in adolescents. This was a randomized, double-blind, multi-center placebo-controlled study of 177 patients who were 13 to 18 years of age.

Of the 220 patients who entered an open four-week titration phase, 177 were titrated to an individual dose, with a maximum of 72 milligrams per day. And this was based on meeting specific improvement criteria on the ADHD rating scale, and the global assessment of effectiveness.

For the patients who met the criteria, they were then randomized to receive their individual dose anywhere between 18 and 72 milligrams per day, and there were 87 patients in that group, or placebo, and there were 90 patients in that group, during a two-week double-blind phase.

The mean scores for the investigative rating on the ADHD rating scale demonstrated that Concerta was significantly superior to placebo in this trial.

In terms of the adverse events associated with this trial, no Concerta patients discontinued treatment, and one placebo patient discontinued treatment due to increased mood, irritability.

The adverse treatment emergent events that were seen in the placebo controlled clinical trial in the adolescents included accidental injury, fever, headache, anorexia, diarrhea, vomiting, insomnia, pharyngitis, rhinitis, and dysmenorrheal. And these are currently in the label.

So based on the initial studies for approval and the additional studies for exclusivity, the current indication in usage for Concerta is attention deficit hyperactivity disorder, or ADHD, is indicated for the treatment of attention deficit

hyperactivity disorder.

The efficacy of Concerta in the treatment of ADHD was established in three controlled trials of children aged six to 12, and in one controlled trial of adolescents aged 13 to 17, and all patients met the DMS-IV criteria for ADHD.

Okay, now we're going to switch gears, and I'm going tell you about the drug use trends for methylphenidate in the years 2002 to 2004.

Overall there was an increase from 25 million prescriptions in 2002 to over 29 million prescriptions in 2004 for single ingredient and combination psychostimulant products.

Methylphenidate products accounted for approximately half of all stimulant prescriptions in the past three years, and Concerta retained approximately half of the market share for methylphenidate products during all three years.

The most frequent prescribers are pediatricians with 37 percent; psychiatry, 31 percent; and family practice, 11.7 percent.

In terms of patient demographics, 80 percent of the claims are for pediatric patients aged one to 16 years of age, and 75 percent of all pediatric claims are to males.

The indication associated with use in pediatric patients is attention deficit disorder in more than 96 percent of mentions during office-based physician visits.

I just want to take you through this graph just for a moment. Over on this side are number of prescription claims. This is number of prescription claims for Concerta by patient age, and this is year 20002, 2003 and 2004.

This first bar here is those patients who are aged two to five. So you can see there is relatively limited use in patients aged two to five.

The next bar does not go as you would logically think, but it goes by increasing use. This is patients aged six to 11, so the pink bars are six to 11. The green bars patients ? I'm sorry, 12 to 16 ? excuse me.

The pink bars are 12 to 16, the green bars are six to 11. So more use in the six to 11 age population that the 12 to 16. And then the blue bars here are actually a total of pediatric patients, so you have an idea of pediatric patients compared to adults. The dark bars here are adults.

So this is all pediatric use. This is adults. This is two to five, six to 11 ? I'm sorry,

12 to 16 and six to 11. Does that make sense? Okay.

Now I'm going to take you through the review of the AERS data that was submitted to the FDA prior to January 4th, 2005.

First, I'm going to actually do a very brief comparison of all the methylphenidate products in the one-year post-exclusivity period, both short and long-acting methylphenidate in children ages zero to 16 years.

Then I'm going to really focus on the Concerta adverse event reports. I'm going to go through the raw counts of the adverse events for Concerta following exclusivity.

I'm then going to do an in depth review of the unduplicated reports for Concerta in children zero to 16 years of age during the one-year post-exclusivity.

And then I'm going to look at the general raw counts of adverse events for Concerta following market approval.

Let me walk you through these a little bit. In terms of the adverse event reports for methylphenidate products in the one-year post exclusivity, we have a total number of reports here. This is Concerta, 135, and later in the presentation

I'll tell you where that 135 comes from, compared to other methylphenidate products.

The other methylphenidate products, as you will see in your review, is a combination of those products that are intermediate and extended release. So you will see this in your review broken down into two subgroups. But I've actually pooled this data for simplicity.

So a total of 96 other methylphenidate ? I don't want to spend a lot of time on these numbers, because I'm going to go into much detail on them when we get to Concerta, but just to note that there are not significant differences in terms of the origin of the reports, in terms of the gender of the reports, in terms of the age of the reports, with primarily the age reflecting what we saw in the use data in the six to 11-year-old population.

In terms of the characteristics of these adverse event reports, there was one death in the Concerta group that actually was confounded with cocaine use, and I will tell you in more detail about the deaths in a moment; one death in the other methylphenidate group; similar numbers of hospitalizations, life-threatening disability requiring intervention; and then other medically

important category.

Okay, to tell you about the deaths in those two patients, the first was the death in a pediatric patient taking Concerta. This was a 16-year-old male who received Concerta for bipolar disorder for two days. Concerta was replaced with Adderall, and seven days after discontinuing Concerta the patient was found in cardiac arrest with cocaine powder in his lap and was pronounced brain dead.

The death in the pediatric patient taking other methylphenidate products was a 12-year-old male who received Ritalin SR from May, 2002, when he was changed to Ritalin LA in July, 2003.

He also received a number of medications for asthma. He collapsed on the playground in August, 2003, and could not be resuscitated. There was no acute history of asthma exacerbation. The autopsy showed mild lung inflammation and cerebral edema, but was inconclusive regarding the cause of death.

I have also added for completeness in terms of serious adverse events a nonfatal cardiac arrest in a pediatric patient who was taking methylphenidate products. This was a 13-year-old male with coarctation of the aorta and two mitral valve replacement who was on the heart transplant list

because of long-standing dilated cardiomyopathy, with a history of sick sinus syndrome and ventricular fibrillation, who received Concerta for an extended duration.

The patient experienced a cardiac arrest, was resuscitated, and had a pacemaker defibrillator inserted. Concerta was discontinued for two more weeks.

Okay, in looking at the adverse events as they come into the FDA, they have been categorized based on what would be the predominant adverse event. And when you look at these, I'm going to go through these for Concerta in great detail, but just to compare them to the other methylphenidate products, once again, the 135 for Concerta, and 96 for other methylphenidate, there are similar numbers of psychiatric and cardiovascular events, although we'll talk in depth about these, and similar numbers of other adverse events by the categories that you see.

Now I'm going to focus exclusively on the pediatric adverse event reports for Concerta in the one-year post-exclusivity period.

I'm going to give you the demographic information first. There were 265 reports for all ages, including ages not specified, of which 144 were

in the U.S. There were 13 deaths ? 13 deaths in the U.S.

Of those 265 reports, 164 were in the pediatric population; 77 from the United States. One hundred and forty-nine were serious, and there were three deaths.

Now you will remember that I told you that there was one death. And the reason why this raw data reflects three deaths is because two deaths were actually in what are described as adults or 17 year olds, and that one death then that I told you about was attributable to the associated cocaine use.

And just so you know, for these kinds of raw data, that does include duplicate reports.

So to drill down into the pediatric event, adverse event reports in the one-year post-exclusivity period, this is the 164 total reports from the previous slide.

There were two as I told you that involved adults. There were five duplicate reports. There were 14 that involved non-Concerta methylphenidate products. Leaving us then with 143 unduplicated reports.

There were in addition eight cases where no adverse event was reported, leaving 135 reports to

evaluate.

There were confounding variables in 19 of those cases, and I want to just describe those to you. The adverse event started before Concerta in one patient. The adverse event started after Concerta was discontinued in two. The adverse event was consistent with a preexisting or familial illness in four. The adverse event was temporal to the use of another drug for which the event is a known effect in seven. And the adverse event resolved during ongoing Concerta use in five.

In terms of looking at the pediatric adverse event report outcomes, there were 77 foreign reports, and 58 U.S. reports. There were 26 in females, 108 in males, with one unknown.

The age range, there were none in the zero to one month, none in the one month to two years, one in the two to five year category, 82 in the six to 11 year, and 52 in the 12 to 16 year category.

In terms of outcome the death ? this was the death that I described to you; 39 hospitalization; five life-threatening; one required intervention; 95 were described either as medically important or other; five disability; and no outcome selected for seven.

The indication for the methylphenidate use

was overwhelming ADHD hyperactivity or ADD; in six patients there was disturbance in attention, learning disability, opposition-defiant, developmental disorder or Tourette's; and in 21 patients the indication for use was unknown.

Okay, now I'm going to take you back to those categories of adverse event reports that we talked about. And this is the 135 reports that have been categorized into the predominant adverse event category.

So psychiatric adverse events, cardiovascular adverse events. So psychiatric adverse events, there were 36; cardiovascular, 20; neurologic, 16; gastrointestinal, 11; hematologic, 10; miscellaneous, 8; special senses, 7; cerebrovascular, 2; overdose of use, 3; lack of effect, 3; and significant confounding variables that I've already presented to you in 19.

Now I've highlighted here in the purple psychiatric, cardiovascular, neurologic, special senses and cerebrovascular, because those are the ones that I'm going to present the data of all the reports, the individual reports.

I have the data for gastrointestinal, hematologic and miscellaneous in the backup slides if

anyone is particularly interested in seeing those, we can do the hematologic ones afterwards.

DR. SANTANA: Sounds like a lot already.

DR. McCUNE: Yeah, I figured that.

Okay. Before I go on, because something that you as a committee hear about in every presentation that we do, are whether something is labeled or unlabeled.

And while sometimes that is very clear, sometimes it's not quite so clear. And I just want to explain to you where ? how we evaluate these events as they come in.

If something comes in and has exact wording as something that is already in the label as an adverse event, that's pretty easy. That's a labeled event.

Then there are events that have similar wording or meaning. In other words someone describes shaking or trembling, but tremors is in the adverse events. And so that would be considered labeled because it's similar enough in terms of its wording and meaning.

Then there are unlabeled events. And these are events which are clearly not labeled in the label, or as Dr. Iyasu talked about yesterday,

something where the severity is more than what you would have expected in the labeled event.

I want to point out that just because something is not mentioned, these reports do not assign causality. In other words, these are reports of patients who have an adverse event, or have an event, and they are on the drug. And I'm going to try to present some data that talks about what Dr. Iyasu talked about yesterday in terms of causality, in terms of challenge, de-challenge and re-challenge information, if we have that.

But many times we don't have that information, and many times it's hard to make the correlation that that is causal in terms of the adverse event.

So not mentioned may mean a number of things in terms of causality or noncausality. But we're including those as saying they are unlabeled.

And then there is this box of adverse events that are reported that are open to interpretation as Dr. Andreason was talking about this morning. And an example of that is the fact that anxiety is mentioned in contraindication, and is that sufficiently labeled in contraindications or does it need to be somewhere else in the label?

And I think what you all talked about yesterday I think was a very good example in terms of the leflunomide label, where someone who is a subspecialist in rheumatology might read that label differently than someone who is not necessarily seeing those patients on a consistent basis.

So I think that there is a lot of discussion to be had within this open to interpretation. So I'm going to present you data where it seems to be clear that things are labeled, and it seems to be clear that things are unlabeled.

And then I'm going to present to you reports, and I'm not going to call them labeled or unlabeled; I'm just going to tell you where you would find that information in the label if you were going to look for it.

Okay, the first thing I'm going to show you in the psychiatric adverse events in the one-year post-exclusivity period are some challenge de-challenge information that we do have from the adverse event reports.

These are the 36 cases that I told you about, and in terms of agitation, behavior disturbance, there were 15 reported cases. And I need to stop here and say that when the adverse events are

categorized, as I categorized them into those cases, they are categorized by the predominant effect. So that a case comes in, you will see 36 cases. But the case may involve a significant number of adverse events that are reported. In other words, one case may have a patient who described agitation, hallucinations, and anxiety. And so for this ? for the purposes of this presentation that would be one case, but I'm going to give you all of the event information, which is why these numbers here don't add up to 36.

In terms of agitation/behavior disturbance there were 15 reported cases, nine of them resolved or improved when Concerta was stopped, or one improved when Concerta was stopped and alternative therapy was given.

There were 12 cases of psychosis/hallucination or visual hallucination, eight of which resolved or improved when Concerta was stopped.

There were 11 cases of suicidal ideation or suicide attempt, five of which resolved when Concerta was discontinued; one of which improved when Concerta was discontinued and alternative therapy was given.

There were eight cases of anxiety, six of which improved after stopping Concerta; one of which resolved when Concerta was stopped and alternative therapy was given; and one which resolved when the Concerta dose was decreased.

Sleep disturbance was reported in six cases, three of which resolved or improved when Concerta was discontinued; one which resolved when Concerta was discontinued and alternative therapy was given; four patients with obsessive-compulsive reaction, of which three resolved or improved when Concerta was discontinued; one case of mania that resolved when Concerta was discontinued; two cases of euphoria, one of which resolved when Concerta was discontinued; and two cases of depression, both of which resolved when Concerta was discontinued.

Okay, this is what I was talking about before in terms of, now I'm going to tell you about what events we saw that were labeled, unlabeled, or in this category that I'm calling reported events.

In terms of reported events, there was anxiety, also described as fearfulness, phobia and panic attack; there was agitation or behavioral disturbance, also described as violent behavior, aggression, self-injurious behavior, crying,

disinhibition, abnormal behavior, change in behavior, irritability, and social withdrawal.

There was psychotic behavior and abnormal thinking that was reported. And I just want to reinforce that in the contraindications in the Concerta label is states that Concerta is contraindicated in patients with marked anxiety, tension and agitation, since the drug may aggravate these symptoms.

And in the warning sections of the Concerta label is states that clinical experience suggests that in psychotic patients administration of methylphenidate may exacerbate symptoms of behavioral disturbance and thought disorder.

Okay. In the label, under events labeled under adverse reactions are sadness, insomnia, anorexia, increased waking, decreased appetite, sleep disorder, and headache.

The events that are labeled under other methylphenidate products ? remember that section of the label that I told you was other methylphenidate products ? were choreoathetoid movements, transient depressed mood or depression, toxic psychosis. And there were reports of hallucinations and visual hallucinations.

Events that are labeled under overdose include euphoria, hallucinations, and then the report was for visual hallucinations; tremor, and the report was for trembling, and one was for shaking.

And the events labeled under information for patients includes psychosis, including abnormal thinking or hallucinations.

And those labels that did not appear to be ? those events that did not appear to be in the label are suicidal ideation, suicide attempt, obsessive-compulsive reaction including trichotillomania, pica and rumination, bad dreams, listlessness, psychomotor slowdown, and mania.

Okay, now I'm going to go on to the cardiovascular adverse events reported in the one-year post-exclusivity period. Once again, I'm going to present you with the challenge de-challenge information we have, if we have it.

And once again, there were 20 cases, but the reports I'm going to give you, the cases may have more than one adverse event reported, so that these numbers are going to be more than the number of cases.

So there were five cases of hypertension or increased blood pressure, four of which resolved when Concerta was stopped. There were five cases of

tachycardia, two of which resolved when Concerta was stopped. There were two cases of syncope, one which resolved with discontinuing Concerta, and seven cases of chest pain, four of which resolved when Concerta was discontinued.

There were also other reports without any challenge or de-challenge information. One patient with left atrial enlargement on EKG; two dizziness; three, headache; four, dyspnea, or dyspnea or exertion; one vomiting, one sweating, one abnormal EKG, two increased QT interval, one supraventricular extrasystoles, and two peripheral vasoconstriction or obstruction.

Okay, now to just try to put these in some context in terms of the labeling, those events that are labeled under warnings are hypertension and tachycardia. Those labeled under adverse reactions are dizziness. Those labeled under the other methylphenidate product section are chest pain, superventricular extrasystoles, cardiac arrhythmia, and AV block.

And unlabeled events for cardiovascular cases include increased QT interval, syncope, left atrial enlargement of EKG, dyspnea or exertional dyspnea, peripheral vascular obstruction with cyanosis

in the toes and peripheral vasoconstriction.

Now I'm going to move along to the neurologic adverse events associated with Concerta use in the one-year post-exclusivity period. And I'm not giving you challenge de-challenge information just in the interests of time, but just to give you where in the label these events are noted.

Events labeled under warnings ? and these were the events that we received ? seizures, epilepsy, focal epilepsy, and absence seizures.

Events that were labeled under adverse reactions included visual disturbance, dystonia, tics, sleep disorder, dyskinesia, restlessness and headache.

Events labeled under overdosage included disorientation, tremor, shaking and confusion.

Unlabeled neurologic events included aching extremities, leg numbness, asthenia, retrograde amnesia, sleepwalking, eye pain, decreased consciousness, and brain tumor and cyst.

In terms of the special senses, adverse events reported with Concerta in the one-year post-exclusivity period, there were seven cases. There was one reported event, and remember, that's that category that I'm telling you is not definitively labeled or unlabeled.

There was an increased intraocular pressure, and in the label Concerta is contraindicated in patients with glaucoma.

The additional special senses adverse events included visual disturbance, transient blindness, loss of color vision, and strabismus and diplopia.

In terms of the unlabeled special senses there were abnormal eye movements, retinopathy, and nystagmus and vertigo.

In terms of the cerebral vascular adverse events reported with Concerta in the one-year post-exclusivity period, there were two cases, one case each of cerebral aneurysm, and an unspecified cerebral vascular disorder with hallucinations.

The cerebral vascular disorder is labeled under other methylphenidate products. And cerebral aneuryism is unlabeled.

In terms of the Concerta timeline we started here in August of 2000 with market approval. In December of 2003 we had pediatric exclusivity granted. And January 4th, 2005, was when we looked, we stopped looking at the one-year post exclusivity review period.

This is the period that I have just talked

to you about in terms of adverse event reporting. In terms of being concerned about especially the deaths in the entire post-marketing period ? now I'm going to tell you about raw events, raw counts of events in the post-marketing period, and then with some detail on the deaths.

The raw counts of adverse events reports for Concerta from August 1st, 2000, through January 4th, 2005, included a total of 936 adverse events for all ages, of which 862 were serious, and 52 deaths.

Of those 936, 642 were in the pediatric population, of which there were 16 deaths. Now you must remember that all of these raw counts include duplicate reports.

Okay, in looking at those 16 deaths over the entire period of time since August 1st, 2000, there were a total of seven unduplicated reports. There were three cases of suicide or overdose. One was a 14-year-old on Zoloft and Concerta who committed suicide. There was a 13-year-old on Wellbutrin and Concerta who died of methylphenidate overdose. There was a 15-year-old with Tourette's and autism on Concerta who committed suicide by hanging.

There were two cardiovascular cases that involved a 13-year-old on Zyrtec and Concerta who died

in sleep, presumably of a cardiac arrhythmia was what was reported.

A 13-year-old on Concerta with a history of syncope who died of sudden cardiac death with polymorphic ventricular tachycardia. And then two other deaths, one in a 9-year-old with a history of asthma on Claritin, Flovent and Concerta, who had viral symptoms with vomiting and coughing and arrested after increased respiratory distress with a very high noted methylphenidate level.

And then that 16-year-old that I told you about who had been off Concerta for seven days and then found dead with cocaine powder.

Okay, in summary, for the Concerta adverse event report profile for the one-year post-exclusivity, there were a total of 135 unduplicated pediatric reports. The majority of use and adverse events are seen in the six to 11-year-old population.

In terms of the psychiatric adverse events, what were noted were anxiety and agitation. The contraindication section states that this is contraindicated in patients with marked anxiety, tension and agitation since the drug may aggravate these symptoms.

Also reported were thought and behavioral

disturbance, psychosis, visual hallucination and visual disturbance.

The warning section of the label states that methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder. The warning section states that visual disturbances have been rarely encountered.

Reports were received of toxic psychosis and transient depressed mood, and these are reported in the adverse events with other methylphenidate products section.

Psychosis was reported including abnormal thinking or hallucinations. And this is reported in the information for patients taking Concerta section of the label.

Suicidal ideation is unlabeled.

In terms of the cardiovascular events in the one-year post-exclusivity period, reports for increased pulse and blood pressure were received, and this is described in the warning section of the label.

Blood pressure and pulse changes both up and down, angina, and cardiac arrhythmia were reported, and this is noted in the adverse events with other methylphenidate products section of the label.

Tachycardia, palpitations, cardiac

arrhythmias, and hypertension were reported, and this is noted in the overdosage section of the label.

Prolonged QT interval and syncope are unlabeled.

In terms of the summary, there is a need to examine the adverse event reports in the other stimulant products with respect to the psychiatric adverse events. There is a need to characterize the cardiovascular risk for all the stimulant products. And there is a plan to revise the label to ensure clarity, so that all prescribers and patients are appropriately informed.

Thank you.

DR. NELSON: For Victor's sake, do you want to just do the hematology.

DR. McCUNE: I'm sorry.

DR. SANTANA: I didn't pay him for that.

DR. McCUNE: I kind of knew it was coming. I think it's my first backup slide.

In terms of acknowledgements, obviously this was a tremendous amount of work done by a large number of people. And I just want to acknowledge all the help that I received on this from the individuals in the Office of Drug Safety, Kate Phelan, Cindy Kortepeter, Kate Gelperin, Mark Avigan, Laura

Governale, Sigal Kaplan, Gerald Dal Pan, and in the Division of Neuropharmacologic Drug Products, Glenn Mannheim and Paul Andreason. And of course all of the people in the Division of Pediatric Drug Development that helped put this together.

Okay. Hematologic adverse effects reported with Concerta in the one-year post-exclusivity period. There were 10 cases. Those events that were labeled under other methylphenidate products included iron deficiency anemia, neutropenia, and granulocytopenia.

There was a report of HSP that would be covered under hypersensitivity, and there was a report of thrombocytopenia, report of petechiae, and of eosinophilia.

Unlabeled hematologic events included hematoma, lymphocytosis, and leukocytosis.

DR. NELSON: Thank you.

We now have about an hour for questions and discussion.

Before we get started, in order to give me a sense of pace, I know we were going to allow time for the sponsor to respond if they so choose. Do you anticipate doing that before lunch? Or are you going to respond after lunch? Or do you want to wait to see

how the discussion goes?

(No audible response.)

DR. NELSON: All right, so we'll just proceed, and open it up to questions and discussion.

Victor.

DR. SANTANA: I have a general question which I think comes up every time I get exposed to adverse events in the raw data and how it's collected and how it's analyzed.

So if you told us that 50 percent of the market is Concerta. So globally when you look at raw adverse events that are being reported voluntarily, given that the drugs act the same way, given that the pharmacokinetic profile is very similar, and assume that there may be some nuances in terms of side effects but not major, you would expect double the number of reports, right, for Concerta compared to the other class of drugs?

And when I look at your raw data, that's not true. Is it because of the way the data, because it's voluntary reporting, it may be completely biased against one versus the other?

DR. McCUNE: As you say, the reporting is voluntary, obviously. It's a small number of the adverse events that we actually capture, and some of

the reporting tends to do with how old or how new a drug is, in other words, something that is relatively new on the market people may be a little more tuned in to reporting an adverse event.

So it's very hard to categorically and quantitatively look at the two of them compared to each other. What we were trying to do was determine whether or not for one, for Concerta versus the other methylphenidate products, even though based on the literature and based on the pharmacokinetics we wouldn't expect any significant difference.

We just wanted to make sure that that was not the case. And within the vagaries of the AERS reporting system it looked like there were similar reports in all of the different categories that we looked at.

But it's very difficult quantitatively to do that comparison because of all the caveats of the AERS reporting system.

DR. NELSON: Mary.

DR. GLODE: Yes, I just had a question about, essentially about toxic psychosis and hallucinations and the label.

So I know that you have said in the label clinical experience suggested in psychotic patients

administration of methylphenidate may exacerbate symptoms, et cetera.

And then you said under information for patients. So I just wondered, I don't have it in front of me, under the information of patients, does it again only refer to people with a previous diagnosis? Or does it say in a normal person toxic psychosis and hallucinations may occur in a previous --

DR. McCUNE: Let me read you exactly what it says from the information for patients section of the label.

It says, what are the possible side effects of Concerta? In the clinical studies with patients using Concerta, the most common side effects were head aches, stomach pains, sleeplessness, and decreased appetite.

Other side effects seen with methylphenidate, the active ingredient of Concerta, include nausea, vomiting, dizziness, nervousness, tics, allergic reactions, increased blood pressure and psychosis, parentheses, abnormal thinking or hallucinations, end of parentheses.

This is not a complete list of possible side effects. Ask your doctor about other side

effects. If you develop any side effects talk to your doctor.

Then the next question says, what must I discuss with my doctor before taking Concerta? And it includes, are you being treated for depression or have symptoms of depression? And also includes: Do you have abnormal thoughts or visions, hear abnormal sounds, or been diagnosed with psychosis?

DR. NELSON: Let me just ask a question to make sure I understand the denominator in terms of prescriptions per year.

So from the prescription use, 29 million single ingredient or combination psychostimulants, of which 50 percent is considered a ? if you imagine ? that would come down to about 23 million overall in pediatrics, which is 80 percent.

So assuming ? and maybe other people know this data ? but assuming that you either have a every-month pharmaceutical plan or a every-three-month pharmaceutical plan, that translates by my math to between one and three million child-years of exposure per year for Concerta.

Did I get that right? So is it a really high level of exposure within the pediatric population to that drug as the denominator for the numerator of

the adverse events, albeit it voluntarily recorded.

Is that fair? I'll ask Judith who might have done the math.

DR. O'FALLON: I've been trying to figure out how to do this. And I've been trying different things. I was looking at the number of prescriptions because that's what they reported to us.

DR. NELSON: Richard?

DR. GORMAN: Just for your divider I think the number needs to be 12, because the Drug Enforcement Agency requires that a prescription be written every month. Is it 12 or three?

(Off-mike voice.)

DR. NELSON: The lower number was 12, so that would be between one and two million exposed. The higher number was if you did it four times a year.

So if it's a monthly, you basically have 23.2 million prescriptions per year in pediatrics, of which then I guess divide that by 12, so you've got 1.7, 1.8 million child-years exposure per year to the drug.

DR. McCUNE: Was Concerta half of all stimulants, or half of all methylphenidates?

DR. MURPHY: I think that's an important point. I think this says that methylphenidate

products were half of all stimulants, and then Concerta was half of all the methylphenidates, right.

DR. NELSON: So it's somewhere in the 800,000 range?

DR. ANDREASON: On your estimate of prescriptions, too, the DEA will allow three month renewals, and it sometimes varies from state to state.

So what, my daughter gets it every three months.

DR. GORMAN: Well, I don't want to say anything, but the DEA is very clear on this. And last November they made it very clear to the Academy of Pediatrics with a specific unfriendly letter. You can write three months in some states if you put in a caveat that, do not fill until such-and-such a date. So you can get three months' of prescriptions at any given time, but you can't get a three month prescription.

DR. RAPPLEY: I write three month prescriptions all the time, particularly for the patients who mail ? who get their scrips by mail.

DR. GORMAN: Somehow the DEA and the out-of-state prescribers, they have not quite caught up with them yet. But they are concerned about drug diversion.

DR. NELSON: We're at a meeting of a different agency fortunately at the moment.

(Laughter.)

DR. NELSON: Let me just ask Marsha a question, and then go to Angela. Your estimate, how do you see just the population exposure to Concerta and to methylphenidates based on this data? What would be your estimate? Are we in the ballpark to say about a million?

DR. RAPPLEY: Well, I think your guess is as good as mine. I would say you're in the ballpark.

It's really hard to get that denominator, and all of the studies look at really exclusive kinds of populations. You know you can get good data on Medicaid populations, but you can't ? and you can get good data through certain mail-in drug pharmacy groups. But you can't get very good data on the whole entire population.

We did that in the state of Michigan, when it was on a triplicate prescription program, but that data was from 1993, and at that point in time the overall use was like around 3-1/2 percent of children, of boys 10 to 12, who were receiving a stimulant.

But that's 10 years ago, so it's got to be higher than that.

DR. MURPHY: Let me just throw in another number. We want to make sure we never reach clarity here. Because there is such variety. The other number, and this was given to me by our ODS people, is that from one of the databases is that the majority of prescription claims for Concerta were for persons one to 16 representing an average of approximately 80 percent of all claims over three years. Based on this percentage they come up with 6 million prescriptions are estimated to have been dispensed nationwide for persons one to 16 during one year. So 6 million a year, and then do your math for Concerta.

DR. NELSON: So that would be then 500,000 child years if you divide by 12. So that would be the lower number. If you divide by four it's 2 million. So it's somewhere in that range depending on compliance with the DEA.

Let me go to Angela.

DR. DIAZ: I'm curious as to why the data for 17-year-olds is not included in pediatrics?

DR. McCUNE: It's a regulatory definition of pediatrics, is up through the age of 16. That just happens to be the regulatory definition of pediatrics.

DR. NELSON: Let's go to Bob, and then I'll come down here.

DR. WARD: As a neonatologist, I don't see these children. And so that leaves me left looking at literature. I make them, yeah. But I found in older reports a general association between ADHD and suicide as well as psychosis. There is no reference as to whether that was at onset of therapy or during treatment.

Is there a recognized association among the psychiatrists between those two? That is, simply suicidality and ADHD? I can certainly imagine that scenario.

DR. NELSON: Do you want to answer that, Benedetto or others?

DR. VITIELLO: I can only say that there is virtual comorbidity, meaning that attention deficit disorder can be co-morbid with mood disorders, particularly depression. And so the concurrent ? concomitant administration of a stimulant to treat attention deficit disorder in the context of a mood disorder is fairly common.

So that is an additional confounder. Then the fact of having attention deficit disorder is, of course, impulsiveness is one of the key components. That may be an increased risk for suicide risk overall and by itself.

DR. NELSON: Deborah.

MS. DOKKEN: Given some of the questions that Dr. Murphy posed to the committee that I guess he'll come to later, I wanted to come back to the patient slash parent information.

And I have just a sort of factual question first, which is, under what circumstances is that included, because it's not always included? And who makes the decision?

And then my second question is, my layperson's impression from some of your presentation was one of the things we need to be thinking about is the clarity of information, that it may be alluded to or in different parts of the labeling, but how clear is it.

So I wonder if you have any thoughts about the question of clarity specifically in the patient-parent information? Does the clarity issue become more difficult when you try to put the information in lay language? I know we have many discussions about well, if you tell people they'll be upset and worried.

So do you find that the kind of open to interpretation lack of clarity issues are more predominant in this patient-parent insert?

DR. McCUNE: Let me answer the first part

of that question, which is that the patient information is actually a ? it's part of the label. It's described as information for patients taking Concerta or their parents or caregivers. That's a part of the label. That is with every label, so that's part of the label, not a med guide. It's part of the label.

And in terms of the clarity issue, it's another place in the label where we have information. I don't think it's less clear in that part. I think it's, as I just read, in terms of the fact that the possible side effects, including psychosis or abnormal thinking or hallucinations, are listed as a possible side effect.

So it's yet one more place in the label, and the question I think this afternoon that Dr. Murphy is going to have you all discuss is, is this sufficient in the various ways that these things are mentioned in the label? Is that sufficient for clarity for practitioners who are prescribing this medication?

DR. NELSON: Michael.

DR. FANT: Yes, I'm asking this question knowing that based on what we've heard I don't think we have a clear relationship between levels and

observed toxicity that we can kind of hang our hats on.

But other cases that have been reported of severe adverse effects, given the dose that the patient was one, and the weight at the time, and you did the calculation to convert it to a dose-per-kilo basis, can you see or get any sense that the reports you're getting are tending toward the higher doses that are significantly higher than what you would optimally base the dose on based on the pharmacokinetic data that we just heard?

DR. McCUNE: We're very limited in the information that we get many times in the reports. And like that one report of the death in the post-marketing period when I showed you the levels were higher than what would have been therapeutic. That was because that information was included in the adverse event report.

Most times we're lucky if we get an age and a sex. Generally we will get the drug name, obviously. Many times we don't get the dosage that they're on, and very, very rare that we would actually get their weight.

So we could go back and look at that, but I think that the data is going to be so sparse that

I'm not sure we would be able to make much out of that, just because of the limitations of the data that we have in the AERS reporting system.

DR. KAVANAGH: I have a slide that actually addresses that.

DR. NELSON: Well, while you're getting up that slide, why don't we ask Elizabeth her question.

DR. GAROFALO: My question is, along those lines in the labeling, there is a description of overdose. So do you have anything from clinical trials or anywhere else that would have some of this plasma concentration information relative to the children that are described here under overdose? Or what more can you tell us about that?

DR. McCUNE: This was overdose information associated with all methylphenidate products. So not specifically for Concerta.

DR. GAROFALO: So you don't have any specific data?

DR. McCUNE: No specific data correlating levels, no. Dr. Kavanagh may have that from a pharmacokinetic perspective.

DR. NELSON: It'll take us a little time technically to get it up, and then we'll talk about that. But let's continue with Victor while we're --

DR. SANTANA: I want to follow up on Deborah's point about the ? in the package insert there is a section for patients and parents, and it's a narrative, because I heard you read it out, and I actually saw it in the materials too.

Is it an assumption that when you read that list, when you see nausea, vomiting, diarrhea, that those are in frequency of order? And is that what most people assume when they read a document like that?

DR. McCUNE: That's a tough question for me to answer, what most people would assume. They're not listed by frequency. In the label there are specific frequencies listed for the adverse events that were seen in the clinical trials.

DR. SANTANA: Oh, no, no. Yes, those tables. I'm saying in the narrative section that you give to patients and parents, when I ? this is me, one individual ? when I read something that is a narrative, and there are 10 things listed, I assume, maybe I'm incorrect, that the first one you mention is probably the most common that I need to worry about, and when I get to number 10, I usually don't worry about that one.

DR. McCUNE: Well, the first sentence does

describe that the most common side effects were headaches, stomach pains, sleeplessness and decreased appetite.

And then the next sentence goes on to describe additional adverse effects, so less frequent, but not then in any particular order.

DR. NELSON: So if Dr. Kavanagh wants to find a microphone, we can at least go through the slides he's referring to.

DR. McCUNE: I'll be glad to give it up.

DR. NELSON: Don't go too far, though.

DR. KAVANAGH: Yes. I can never remember details of slides, but I'm sure you can. But on my history of methylphenidate, in Goodman and Gilman it talks about these reactions occurring early in therapy and being idiosyncratic. You can't predict prior to someone going on the drug who's going to have it, and typically, if you see it very early in therapy when someone is just starting it, or as you're titrating the dose up, to what's a tolerate dose and whatever. And that makes sense.

We expect that if you push the dose on everybody, everybody will get it. If you overdose to whatever degree. And we don't know where that is, whether it's 200 nanograms per mill, 300, we don't

know.

But that, we expect that. We're talking about these relatively low concentrations, and so you're probably talking about, well, what is the sensitivity? We also, you know, as I said, you're worried about what is the weight in the kids, and are they different.

What I did is, we get annual post-marketing reports, and we look. And so I pulled what was available to me electronically about a day or two ago, and in a six-month period there were 22 reports of acute psychosis in children, one adolescent. Of these 22 reports, you know, I mean it's sometimes difficult to determine whether or not these are actual psychosis or something else, and the terminology is different. So I was using liberal definitions to possibly capture as many possibilities as possible.

And in that case I got 22 maximum. Of those, as I said, one was really not clear if it was psychosis. In other words, there was a really a strong possibility, even though it was termed psychosis, that it was really something else.

Nine of these had confounding variables. One had no dose reported. And that brought us down to 11. Of those other 11, none of those had confounding

variables that were reported. That doesn't mean that there weren't any.

Of the effects of these 11, six were after dosage increases, and two were after the very first dose.

So what I did is, I had weights, and I had dosages for a lot of these kids. And I assumed average weight per age. And here's kind of the average dose, about .9 milligram per kilogram; here's the .8, here's the 2. And you see that assuming average milligram per kilogram dose the effects fall within the usual clinical dosing range.

So which kind of goes back, and is consistent with the old review literature from the '60s, '70s, whatever.

Idiosyncratic ? give a kid with ADHD a normal dose and some kids unexpectedly will have it.

Well, there was one child here who had a slightly higher dose of 54 milligrams. This was a 6-year-old as I said who got the highest ? you know, someone was pushing the dose.

If you change the assumptions, well, what about if you change the assumptions and these kids were super, super lightweight, and ? can you click that? ? and yeah, the milligram per kilogram dose goes

up, but you still ? you know, most of these kids ? the vast majority, like half to two-thirds of the kids are still within the usual therapeutic dosing range of possibility.

And in fact one individual, I mean look at this individual. This is a 16-year-old who had a psychotic reaction with the very first dose at .3 milligrams per kilogram per day. And this was an individual from a drug study.

So you just can't predict. So obviously that individual, it was very clear that that individual really had ADHD, clearly was diagnosed with ADHD, was screened for confounding variables, and still, at the very lowest dose, at the very first dose, it occurred.

So yes, we push the dose. Eventually everyone will get it, but it can occur with normal dosing unexpectedly.

DR. NELSON: Bob.

DR. WARD: In the subject you just referred to, who was in a drug study, did we have actually measured concentrations?

DR. KAVANAGH: No, we did not.

DR. WARD: Oh, okay.

DR. NELSON: Tom.

DR. NEWMAN: With all of the limitations of these adverse event reports, where you don't know the dose, you don't know the child's weight, I don't know the numbers, but my guess is, there must ? I don't know, are there like a thousand or more of them, a thousand children who have been studied in randomized trials of these drugs? And has no one done any kind of meta-analysis to look at the absolute risk or absolute risk increase for various side effects to be able to tell, not only is it causally related to the drug, but what the actual risk is from looking at the randomized trials.

And in all those trials I assume they measured height and weight, because height is something that people are worried about. So then you could actually see whether there was any relationship between the side effects reported in the randomized trials, and the milligrams per kilogram, or milligrams per meter squared dose.

DR. KAVANAGH: That's a very good question. It's going to be ? let me explain some of the limitations there. One is, this is a very old drug which has been approved for a long, long time. And because it works so well and so clearly in ADHD, you need small numbers of individuals in these

studies.

So actually the Concerta data that you saw, 106 in one, 90 subjects in another study, these were actually huge numbers for these studies. I mean, absolutely huge.

And it's basically presumed in terms of safety and everything else, a brand new drug that we'd never given to people before we're going to study much larger numbers. For a drug that's on the market, and we're just changing the formulation, you're not going to do large safety studies to just look at side effects.

The other thing is that these things occur, as I said, when you're starting a dose or starting the drug, or when you're increasing the dose up. A lot of these studies were basically, the kids come in and they're already stabilized on a dose. It's not that they're de novo, so they're just being switched from a dose that they're already on to something else.

In this individual, .3 in a study, my guess is that this particular individual was de novo, so even, and a lot of cases, as you look at these case reports and everything, and these are case reports, the vast majority ? a lot of these individuals, or

several were first doses, within four hours of taking the drug you got it, and then it went away. Or a lot of them were basically, they were on a dose, they were doing well on a dose, and it was decided to increase their dose. Let's see if we can't do a little bit better. And so there were several of these subjects with a new dose a week later, with the variability, whatever, they had an episode. They decreased the dose back down, presumably they're doing fine.

So kind of hard to get what the actual numbers are, but my guess is, with new patients or with increased ? especially new patients, it's not going to be as I say rare. Okay? I mean as I said, these are small studies, and we're seeing a case or two with the NDAs, so that's not rare. It's not real, real common, but it's probably not rare either.

DR. ANDREASON: I'm sorry, I got called out earlier during your question, would you say it again, just because I got the message that you were curious about a meta-analysis?

DR. NEWMAN: It just seemed to me that given all the limitations of the adverse drug reports that there must have been many randomized double blind trials where number one you can attribute causality because you have the control group, and number two,

you actually know the height and weight and the dose and the timing of the side effect in relation to the dose and milligrams per kilo or milligrams per meter squared.

So I was just wondering, could someone put together the randomized trial data and come up with absolute risks of these various side effects, because that would be what would be most informative to the patients and clinicians, the absolute risk increase, the confidence interval, and which ones were really seen in the randomized trials.

And I hadn't realized, maybe all the trials have been small, and maybe a large number of them start with the run-in period so that everybody who has side effects with the first dose was eliminated or something like that.

But still there are a lot of these preparations, and if all them needed randomized trials, there must be at least hundreds, if not a thousand or more kids that have been in these randomized trials.

DR. ANDREASON: Well, let me see if I can answer that. A lot of the trials have taken place over years, since 1955. I think the threshold for reporting adverse events has really changed, just like

the threshold for attributing some of these adverse events to drug has changed.

I think nowadays people are more sensitive. For example, just as there was no adverse event reporting system, people were not particularly clear about reporting sometimes these adverse events during trials, and did not necessarily report them the same way that we do now.

Also, during the trials that have come in recently, these events are very, very rare, and I suppose it would be possible to do a meta-analysis on some of the ? on the trials that have come in over the last say 10 years. But I'm not sure what more we would learn.

DR. O'FALLON: He's asking for the trials.

DR. ANDREASON: Oh.

DR. NEWMAN: We would learn the absolute risk, right? Because we would know the denominator. And we would learn the dose that they were on in milligrams per kilo, which we currently don't know, and we'd be able to see whether there was any association between those.

DR. RAPPLEY: I think the closest that comes to that is a technical report from the Academy committee on the treatment of ADHD, and they don't

come forward with a risk, predicted risk. And part of that is, it's probably the most complete review of all studies ever done in ADHD, treatment studies. And the reason they don't declare a risk is for what ? the reason that Paul just stated, that there was so few studies that actually met the kind of criteria that you'd need to be able to do that.

But the largest study is the MTA study as far as I know that had over 500 subjects enrolled, and they were in treatment for 14 months, and they were followed for an additional 10 months. And I don't want to misquote that, so I want to try to find out maybe this afternoon I can speak to you about the serious adverse events for a very few. And then there were over 100 studies in the Abikoff study in Montreal and New York City, 100 subjects, and it was a similar kind of thing. They were followed for 24 months.

So I think the Academy committee on treatment tried to come as close as ? they came as close as they could to doing that, and maybe over the next 10 years we'll be able to do that as we have that more specific information.

DR. MURPHY: And Tom, actually, we did ask that question, and they did go back. I mean Dr. Mannheim, you don't see what didn't come up. But

because of all the tremendous variability in the way trials were conducted, they actually said we do not think it would be very informative.

I think your point being maybe if we have more recent studies where we have more set criteria, and if we have ? that that might be something we should look at for the future, I think we can take that.

But we did actually go back and try to see if we could gather additional data, and I think it's been pointed out by a number of people, what some of the caveats of that were, because of the tremendous changes in the way that some of these trials have been conducted.

DR. NELSON: Before going to Benedetto and then Judith, let me ask you two questions about what data you see or don't see.

There were 43 adolescents who were dropped out during the entrance to the titration phase. So if you consider eligibility to be at the time of, when they reach the steady dose, the question is, do you get information about those adverse events ? maybe they dropped out just because they didn't want to do it, or maybe they dropped because they in fact had some early side effects that were found. So question

one is whether you get the information about what happens to those who drop out just for review? And the second question is whether you actually ? it was my understanding from past discussions that you often get group data and not individual data and so that asking questions of meta-analysis is something that in fact is very difficult to do within the Agency, only because of the way that the data is seen as far as being able to prepare for those trials. And until you actually get that kind of individual data it's very difficult to do that kind of meta-analysis, at least that's the lesson I took away from the whole anti-depressant discussion.

So I guess it's two factual questions, and then I'll go on to Benedetto and Judith.

DR. ANDREASON: Yes, I think I can answer that question. We do look at adverse events from the time we start taking the drug, so even if they haven't reached their target dose, we still count those adverse events.

When someone drops out, we also look at why they dropped out, even beyond the categorization of, for an adverse event, or patient choice. We try and chase down whether or not the categorization is actually correct, because sometimes patients who drop

out or their drop out reason is placed under the category of other or withdrew consent are actually adverse events. So we do keep an eye on that.

And that was one of the things that we really did look at in the suicide analysis, suicide-related adverse event analysis.

One of the things that actually helped us in bringing that back is an analogy. One of the things that really helped us in the suicide-related adverse event analysis is that the rating scales that were used in those studies actually had a suicide item. And so it was something that we were actually actively tracking, and had information on, and we had been doing systematic analyses of that as an adverse event profile for years in the studies. In the ADH trials, there is no rating scale that looks at that specifically, so we would only be doing with spontaneously reported adverse events, so that would make that particularly difficult.

DR. McCUNE: Can I just add to the exclusivity study, that the study was of 220 patients who entered the four-week period, and then what I presented was discontinuation of treatment for whatever reason. But the 177 that were in the trial were those that were able to be titrated to an

individual dose based on meeting the improvement criteria. So there was not just of those 220, it wasn't just people who stopped because of an adverse event. It was people that were not able to meet that improvement criteria. Because they had to meet the improvement criteria to then go on to be randomized to either continue the drug or withdrawn.

DR. NELSON: Thanks for that clarification.

Benedetto.

DR. VITIELLO: About trying to estimate the incidence of ? you mentioned about psychosis in particular. I think it's very difficult even with a large study, indeed, the MTA is the largest study with about 600 children, randomized, about half of them were exposed to stimulants. And I was part of a study, and I think there was maybe one or two, no more than two actually subjects who developed a psychotic reaction but was transient during treatment, none of the placebo. Actually Dr. Larry Greenhill, who is actually ? wrote our report on this is in the back of the room, so Larry, you may know by heart what the right ? but I think it certainly is below one percent based on that estimate.

The confidence interval I don't think it

can be produced unless you have more studies.

DR. NEWMAN: Actually it can be, and that's really helpful information. One or two out of 600 is useful information.

DR. NELSON: Judith, and then I'll ask if the committee is interested in hearing Dr. Greenhill on this point. Or he'll be in the public session as well, so we could also question him then. But think about it.

Judith.

DR. O'FALLON: A follow-up to what you just said, even a one percent occurrence when there are six million prescriptions a year or something like that, I mean we're looking at serious effects here.

My concern, and what I wanted to say was, my take home message after that whole business with the SSRIs was that the lack of terminology, common terminology accepted, covered up a whole lot of occurrences, that things were simply reported in ways ? or in some cases just not reported, because they said, oh that's just part of the underlying disease.

And I think that there is even in well conducted trials there has to be something done about the standardization of terminology in order to collect that data. I think we have a serious case of under-

reporting not only in the SSRIs but in everything else.

DR. NELSON: Before going to Bob, let me ask Michael, I think I skipped you when we got off on this other tangent. So Bob, you're up and then I'll go to Michael.

DR. BIER: One of the things that struck me is that this is such a frequent diagnosis and treatment that there are some captured populations whose data are available. I'm thinking of the Kaiser plan or in Rochester, Minnesota, the Mayo, where we have really a population basis that's captured, where we could actually look at that information about especially suicide and attempted suicide is such a dramatic event I would think it would be well described.

And I don't know what to do about the terminology of psychosis. Maybe that is well enough accepted that that might also be in their data. But to look over the last five years, when these have been widely used at the beginning of therapy, and then in a six-month or 12-month period, how many of them had these dramatic effects. And that would be useful data that I think would put it on a more solid basis that our voluntary reporting system we're currently relying

on.

DR. NELSON: Michael.

DR. FANT: Yes, I deferred, because my question is going to shift things just a bit. But it looks on the flip side of the issue of individual responsiveness to a given dose or a regimen of the drug.

In terms of intrinsic responsiveness of the individual patient that leads to an idiosyncratic reaction, ultimately we may be left with some intrinsic genetic polymorphisms or something that we really can't define easily that could do it. But some things may be iatrogenic, and this may be a relatively naïve question, but just thinking about kids today, they consume an awful lot of caffeinated beverages everyday, and as they get into adolescence, Starbucks is on every corner. So is there any potential for caffeine levels or caffeine-related compounds potentiating the effects of these drugs? And if there is, is that something that needs to be at least thought about as we move forward trying to understand the toxicity of these compounds?

DR. ANDREASON: For me?

DR. FANT: Anybody. Anybody.

DR. ANDREASON: From my FDA position I

don't have any data on that. From a clinical position one would assume that there would be some kind of an interaction. Caffeine is a stimulant. These are stimulants. You put them together in high enough quantities, something is going to ? ultimately there is going to be a problem.

There are ? for example, and this is what I tell my patients ? there is a given dose at which they will have all of these side effects. And there is one person in the population who, at this dose, will probably have some of these. And we don't know who those are. But if ? so if they combine things that have similar pharmacologic actions, I think one can assume that there is an interaction.

At what point that takes place is very variable. I've seen people have these types of reactions on caffeine alone, when they take it in capsule form, and there is, from tox screens in the emergency room. So it's highly likely that people could combine these and this could happen.

DR. NELSON: Dennis.

DR. BIER: I'm just trying to struggle with a handle on the background noise level. I mean we heard a minute ago about one percent as a significant number among a million or six million

children, which I would agree with. But if we take a million or six million children, what is the background noise? If we just follow a million children who are taking nothing, I mean when I listen to the national statistics on all diseases, I discover that each American has at least two or three major diseases.

So I'm curious what the background noise level is.

DR. ANDREASON: The lifetime prevalence for schizophrenia is somewhere between a half and one percent. And schizophrenia alone. And that doesn't account for bipolar disorder, which is kind of on the same order.

So these are very common symptoms in the population who are not taking stimulant products.

Dr. Biederman, Joe Biederman, has a literature on patients with ADHD who may be even misdiagnosed, I should say with bipolar disorder, childhood bipolar disorder, who may be misdiagnosed. And we consider bipolar mania a psychotic disease.

So it's highly likely that kids who are having trouble in school are brought in, they're evaluated. Attention deficit disorder in many ways is a diagnosis of exclusion. And they may be kids who

ultimately develop bipolar disorder, but at that point in time they receive the diagnosis of ADHD. You want to make a treatment intervention. A stimulant is a very reasonable first line choice. You give it to them, and their nascent bipolar disorder or psychotic disorder comes through.

And then when you pull away the drug, it may become subclinical again. But that doesn't necessarily mean that they are normal kids who have had this response, because something brought them into the pediatrician or to the psychiatrist in the first place.

DR. BIER: I'm really not asking that, I'm asking if I take one million kids who are not diagnosed with ADHD, who are not on any medications, and you watch them for a year, what's the background noise on some of these complications? How many do we expect to see commit suicide?

DR. ANDREASON: That one I can't answer off the top of my head.

DR. BIER: Do we have any evidence that we have a signal above the noise on these small number of events?

DR. NELSON: I'm going to go to Marsha and then Richard.

DR. RAPPLEY: Just to shed some light on the dropout, the people who drop out, you might go back to the early study on the OROS methylphenidate which looked at 312 kids, 213 exposed to methylphenidate, and it was a similar number who dropped out. Of 15 who were exposed to the OROS who dropped out, 11 of them were for lack of effect, not for adverse effect, and exposed ? similar numbers exposed to the immediate release, 10 dropped out for lack of effect.

So that brings your number of dropouts for adverse reactions to a much smaller number than actually dropped out.

DR. NELSON: Richard.

DR. GORMAN: Back to the adverse effects of this particular drug. It was very reassuring to me to see that Concerta and the other agents in the methylphenidate class had similar breakdowns. If we had a similar slide put up of methylphenidates versus the dexamphetamines salts, do we have a feel for, would the data look the same in terms of the relative ratios of those side effects? Oh, excuse me, adverse events.

DR. MURPHY: That's a question we're trying to answer.

DR. NELSON: Marsha.

DR. RAPPLEY: But we do have the Agency for Health Care Policy Research, although I'm probably not getting that title correctly. They had a technical report from a few years ago which looked at that very question, and found the profiles to be very similar, the adverse reactions, between the two types of classes.

DR. NELSON: Benedetto.

DR. VITIELLO: Just a specific question about the prolonged QT interval event that was reported. Apparently this is called unlabeled, meaning that this was not reported on any other ? with any other methylphenidate preparations. This is ? was this specific ? was reported only during the use of Concerta.

DR. McCUNE: No, just meaning that it is not specifically in the label as prolonged QT.

DR. VITIELLO: So even the plain Ritalin does not have that kind of information on the labeling, as prolonged QT. So over all these years of use of Ritalin nobody besides Concerta, nobody has ever pointed out a prolonged QT as an adverse event; is that correct?

DR. TRONTELL: I think you may be

confusing the adverse events from labeling. Perhaps I'm misunderstanding your question. There was an episode of QT prolongation reported for Concerta, but there was not any mention in the product labeling that that was associated with Concerta, or I'll ask Dr. McCune to specify if that's also true for the other methylphenidates.

DR. ANDREASON: Benedetto, I think that's true. I don't believe QT prolongation has been mentioned in any of the methylphenidate product labeling.

In a product that we just looked at and actually QT prolongation is something that has become very interesting to everyone, including the Agency, within the last 10 years, so again, within my professional lifetime.

So looking at it in the methylphenidate products has been something that has been relatively new, and when I say relatively new, I still mean within my lifetime.

One of the problems with looking at QT prolongation in these drugs is that these drugs, stimulants in general, and methylphenidate in particular, increase the pulse. So when you do a QT correction, you've got to use a Federici correction

and not a Bazett.

I'm not sure whether this QT prolongation was measured, was measured with a Bazett or with a Federici. If it's just an automated correction it's probably Bazett, because that's the way all the formulas are. I mean that's the way it is on my Palm Pilot with my program. And I know in order to do a Federici we have to do it in house.

So we looked at the EKGs both pre and post-treatment, and we saw absolutely no signal for QT prolongation in the methylphenidate products, in either the children or the adults, or the limited number of adolescents in the last submission that we looked at.

DR. VITIELLO: So it seems to me that it is not very plausible that methylphenidate indeed, it was because of this prolongation of the QT. Most likely it was not.

DR. ANDREASON: Based on the information that we have, no. But given that methylphenidate has been on the market so long, it hasn't come under the same kind of scrutiny as we have developed more and more standards, especially ? it's kind of an oxymoron, standard special tests ? QT prolongation and the exploration of QT is something again relatively new,

and we're asking companies to do ? oh what is the word ? thank you ? thorough QT studies, and that has been the plan with the stimulants as they come along, we're going to be asking people to do that.

DR. NELSON: But I gather that was not done in the Concerta adolescent trial for exclusivity?

DR. ANDREASON: No.

DR. NELSON: So I guess before asking for other questions, I've heard two themes that I take away from this. One is the difficulty of interpreting rare events, which seems to be a common theme, and the suggestion of different databases, and population-based studies, et cetera. And the other is the complex relationship between patient and drug that you raised in terms of the uncovering of possible comorbidities, and in that case, where do you assign cause? It's still happening, and it's still a problem. Is it the drug? Is it the person? I mean it's just a complex question, perhaps not even answerable, if in fact the overlap in those populations within a psychiatric diagnostic paradigm is extensive enough, you may feel that it's just not something you can tease apart, and that it would be a possible ? you know, you ascribe it to the drug only because of the caution that you would need to give to

clinicians who are then prescribing it to that population.

But that's my nonpsychiatric take on that discussion, just two themes that I have heard in our conversation.

DR. ANDREASON: Just a follow up to your question, you said, was that done on Concerta, I assume you meant a thorough QT study.

DR. NELSON: Or even EKGs.

DR. ANDREASON: EKGs were done. We did look at those. We saw not QT prolongation signal.

DR. NELSON: All right.

DR. ANDREASON: The second part is that given that these are dopamine agonist drugs, and if somebody does get a psychotic episode from a clinical standpoint, at least the way I approach patients, is that it doesn't really matter whether it's the drug or a nascent disease, we've got to pull them off. And if they happen to get better from a de-challenged standpoint, it tends to point at the drug. But from a clinical standpoint I'm going to be watching that patient much more closely.

DR. NELSON: Right, but I guess to follow up at least the logic of my comment, if you had say a disease that was very clearly diagnosable, and then

you had a drug given to someone who was misdiagnosed, you may not label that as an adverse event for the drug, because it's in the context of a misdiagnosis. But if the overlap in the phenomenology of these conditions is so extensive to where it would be almost impossible apart from the drug challenge to notice that there is another comorbidity that would be then uncovered, it may be inappropriate to apply that kind of more simplistic paradigm of mis-diagnosis to considering this an adverse event. That's kind of where I was headed. Does that make sense?

DR. ANDREASON: Perfect sense.

DR. NELSON: Let me ask at this point, other questions to discuss? We can always break for lunch a little early. Are there any desires on the part of the sponsors to comment at this point? There is the open public hearing after lunch that you can certainly formulate.

They're going to wait.

Well, what I would recommend then is, why don't we stop 10 minutes early for lunch, but since we're going to do that, let's start early after lunch. And my suggestion, instead of starting at 1:30, how about 1:15.

Lunch is across the street, which people

that were here before know. I might add, we'll start at 1:15 with the open public hearing, but we'll offer an opportunity at 1:30 as well. So we'll start at 1:15.

(Whereupon the above-mentioned proceeding went off the record at 12:22 p.m. to return on the record at 1:17 p.m.)

ACTING CHAIR NELSON: Before I read the statement that needs to be read prior to our public hearing, one question and one comment. First of all -- and I'll ask the question again at 1:30. Our open public hearing is scheduled to start at 1:30. We're going to start early, so what I'll do is I'll -- after people present, I'll ask again if there's anyone else who wants to present, in case they've come in at 1:30 expecting that to be the time of our session.

Before we get started, just so we have an idea of pace, if I could have a sense of how many individuals have requested to speak during the open public session. I know of Dr. Greenhill. Sponsor?

SPONSOR REPRESENTATIVE: We're waiting for the rest of our team.

ACTING CHAIR NELSON: Okay. I just want to get an idea of heads. Okay. And anyone else besides those two? Okay.

Dr. Greenhill?

DR. GREENHILL: Yes.

ACTING CHAIR NELSON: Are you ready?

DR. GREENHILL: Yes.

ACTING CHAIR NELSON: Oh. I've got to read the statement. Sorry. You're ready, so why don't you go ahead. But I'll read the statement.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the sponsor, its product, or, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the Committee if

you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

And so before you get started, we're going to have to sort of keep people to around 10 minutes, but I think we do have some flexibility. But just so you have an idea, I'll keep time and we'll see how it goes.

DR. GREENHILL: I will follow the protocol. My name is Larry Greenhill. I am a Research Psychiatrist II Child Psychiatrist at New York State Psychiatric Institute. I do have apparent conflicts of interest. I was one of the researchers that worked on the Concerta registration trial, and I've worked as a consultant for them and other companies that have sponsored or have stimulant products on the market.

My travel today has been supported by the American Academy of Child and Adolescent Psychiatry to attend this meeting. And I'm speaking for myself and also hopefully for the American Academy of Child and Adolescent Psychiatry.

We see this FDA hearing as an opportunity to broaden understanding and appreciation for

treatment, both the risks and the benefits, and any clarification and updating and upgrading of the MPH label is strongly supported by our professional organization. And we will hope to benefit from participating in this meeting to help -- to inform our members in our practice parameters of any conclusions that the panel draws.

I'm going to be brief in my comments. As I mentioned before, I think it's a very good thing that the FDA is reexamining the methylphenidate label for safety, and this we hope is a growing trend -- to be more interested in the safety monitoring in terms of psychotropic drugs, as well as all other treatments in the United States.

But at the same time we want to caution about the current state of the art in safety monitoring -- that evaluating a signal from spontaneous reports or a passive surveillance system has its strengths and weaknesses. All adverse events should be, as the panel is doing today, evaluated in terms of a denominator, so that not just severity but the frequency of the side effect needs to be appreciated for both clinicians and parents to be able to do the important benefit-to-risk ratio calculation before entering into a treatment.

And I want to mention some of the studies that we've been doing. The challenges of interpretation have been mentioned before, but some of the problems that are faced by the AERS database are the problems of estimating underreporting, duplicate reports, and some attempt was made to deal with that today, that clinicians don't use a standardized method for approaching parents and children when they ask about side effects. They don't have the training in clinical trials or in practice. There are wide varieties of methods for obtaining that.

And when they get the side effects, they don't necessarily code them in a standardized fashion, so that we may be getting more reports or fewer reports. It's hard to know. That was seen in the antidepressant data when that came in.

Trials are designed primarily for efficacy, but they're grossly underpowered for safety estimates. And we can't tell right now from the AERS database, because of these challenges, how specific a signal is or how strong a signal is. All we know is there may be a signal for safety that needs to be further evaluated.

Now, co-morbidity is another thing that can make evaluating the signal for safety and the

impact of the medication difficult. The rate of co-morbidity in ADHD is very high. What you see here is a Venn diagram of the ADHD sample of 579 children, and only about a third of them had pure ADHD.

But as you can see, they not only had one disorder such as opposition defiant disorder, but a number of them had multiple problems with mood, anxiety, Tourette's, tics, and conduct. And the interaction with methylphenidate with those disorders is a complicated one if a child has multiple disorders.

You heard the panel discuss the need for a denominator, and I wanted to add one other refinement to that, and that's something that came up in the discussion of antidepressants from evidence-based medicine. If one knows the number of subjects you have -- patients you have to treat to find a benefit, and also the number you need to harm, then you have a better chance of evaluating the risk.

And if I were to do the calculation based on the data we got from the MTA, we only -- we found that we would increase the benefit in an ADHD patient treated with a Ritalin treatment, a behavioral treatment, or the combination, over what was done in the community.

So if we just gave them methylphenidate -- and it was the immediate release methylphenidate -- the rate of response to become an excellent responder, that's almost normal, so they couldn't be told differently from a parent or a teacher from a child who didn't have ADHD, about 55 percent of the sample showed that level of improvement. If we added behavioral treatment, then we were able to increase that a further 10 percent.

So we if make the estimates -- and I'm going to do it in a very crude fashion -- I would have to treat two or three children with a methylphenidate product with these kinds of data that came out of the MTA study before I would see one that improved, not only improved a little bit but improved substantially.

And in terms of a psychotic reaction, it's hard for me to do the calculation, but it's well over one in 5,000 patients would have to come into my office before I would see a psychotic reaction, on average. Now, that's a severe reaction that's of great concern to parents and children -- parents and physicians. But if it's seen infrequently or even rarely, it has a different weight than one that's seen frequently.

Now, the other thing is that I'm really

happy to see that you're looking for challenge/dechallenge data to try to draw a stronger link between the medication treatment and the side effect. In the MTA, what we looked at -- and these are side effect forms for immediate release methylphenidate. It was given in a double-blind fashion in a Latin square design during the titration trial.

We saw -- and you can see the stepwise increase in these bar graphs from placebo all the way up through the high dose for appetite suppression, insomnia, and dull lethargy, whereas irritability, which was thought to be an effect of methylphenidate, actually decreases, according to parents in this double-blind trial.

The same thing was seen with teachers. The teachers were not able to pick up these adverse events, but they did see this decrease in irritability in this sample of 288 children who were in this double-blind trial of different doses of methylphenidate. As the doses increased, the irritability went down, suggesting to some of us that the irritability may be a part of the disorder, not a reaction to the medication.

Now, it's good that the psychotic reaction

will be highlighted and put in clear language, and I also urge that there is more information on some common adverse events that we're picking up in our university-based clinical trials.

And this is a -- this is from the MTA study where approximately 145 individuals were each randomized into pure behavioral treatment without medication, community comparison, medication management, or the combination of behavioral and medication.

Medication, as I indicated, was immediate-release methylphenidate in doses between 15 and 60 milligrams a day total daily dose. And if you look across the -- these are the growth rates in terms of mean weight gain. You can see it in behavioral treatment that 112 children who were measured grew at 4.3 kilograms a year, and those on medication 1.9 kilograms.

And the same kind of differential exists for height during the first year of treatment. And the reason this -- I'm mentioning this, this is the first study where we've had 14 months following an ADHD child randomized prospectively off of medication to be able to use as a control group.

And you can see the effects. The upper

curve there with the triangle is the growth rate on behavioral treatment versus the medication treatments, and there's a very weak dose-effect relationship, inverse dose-effect relationship, for the amount of medication dose versus the growth rate that we saw in the sample.

Now, the last thing I'd like to mention is that I am really delighted that there's going to be a review of the MPH label, but I'm encouraging the agency not to stop by -- in the safety section, but to examine the warning section.

There is an anomaly that a number of us became aware of when we started to do a trial with preschoolers, that methylphenidate -- there's a warning on the label against its use under age six. There are approximately 250 kids in randomized trials through the years on methylphenidate in that age range. These are controlled trials.

But there are, as far as I can tell, no randomized trials of preschoolers with the amphetamine, yet it is approved down to age three. It would be useful to bring this up at some point for review, to make it consistent across the different stimulants.

And just to support what Dr. Rappley has

found, we found that we had a higher rate of adverse events in our preschool prospective randomized trial of 165 children that was NIMH supported, running about almost nine percent, slightly higher than the school-age. And the different -- somewhat different pattern, more crying, irritability, and emotional outbursts in this group, and I think Dr. Rappley had indicated that very clearly.

And we looked again for dose proportionality, and we found it for emotional outbursts and also for falling asleep and appetite decrease. So this is in a group of children with ADHD ages three to five and a half, and the growth suppression was seen also.

A small number of them were entered into a study and compared to school-age kids, and what we found -- and I'll just summarize this -- a trend towards there being slower clearance in the very young children versus the school-age group, which meant that there was a trend also for greater exposure at lower doses for children who were very, very young. And this kind of differential for age at some point would -- needs replication, of course, but would be helpful to clinicians and families.

So, in conclusion, from that study I just

want to indicate that our best dose was lower for preschoolers than school-age groups, .75 milligrams per kilogram per day of immediate release methylphenidate versus the .9 that you heard about. And that we found a higher number of patients discontinued because of methylphenidate-related adverse events, supporting what Dr. Rappley said.

So, in conclusion, I want to emphasize the importance of this meeting, its transparent process, its focus on safety, which is extremely important. But I urge the Committee to think about making the clarification information that's going to be recommended for the agency to put in a label to keep in mind not just severity but prevalence, and for the agency to be thinking about prospective studies to explore ways in which the adverse events that are now being detected in the Concerta data can be looked at.

One place that might offer an opportunity is the NIMH and American Academy of Child and Adolescent Psychiatry's large, simple trial that is now underway with 250 practitioners, and some of these side effects might be looked at in that sample. It's going to have several thousand children in it.

Thank you very much for the opportunity to speak.

ACTING CHAIR NELSON: Thank you.

I guess if there's a clarifying question, we could ask it now. Otherwise, we can always ask questions during our discussion.

Okay. I guess -- are there other speakers besides the sponsor? Has all of your party arrived?

Okay. Dr. Adelaide Robb. And you can say more about yourself when you get up there.

DR. ROBB: In terms of disclosure, I am a Child Psychiatrist at Children's National Medical Center in Washington, D.C., so I drove myself here and nobody flew me in from out of town.

I am a member of the Pediatric Psychopharm Initiative Committee for AACAP, and I am the Psychiatric Representative to the American Academy of Pediatrics Committee on Drugs.

I have conducted trials in ADHD for Eli Lilly, Shire, and for McNeil. And I wanted to just talk a little bit about clinically what we -- I don't have the fancy slides; Dr. Greenhill had all of those for you. But I wanted to talk as somebody who actually takes care of patients every day and patients here in Washington, D.C., about how frequently we see hallucinations in kids on a variety of medications, because I think that was one of the biggest concerns

that people were talking about was how much these medicines precipitated hallucinations in kids.

And if you think about it from a pharmacologic point of view, many medicines that work on the dopamine system at certain doses can cause hallucinations. If we think about adult patients with Parkinson's disorder who go on Levo and Carbidopa, you are frequently caught as an adult neurologist between control of the ability to move versus the presence of psychotic symptoms, and they walk a fine line.

If you think about Buproprion, which was first approved at doses over 450 milligrams, and besides seizures being one of the more common side effects, hallucinations were also a common side effect. And then, the dosing regulation was changed to 450 milligrams or less, and in the immediate release preparations 150 milligrams at a time.

Despite having the new dose for Wellbutrin, we still have patients who experience hallucinations at normal doses. And as somebody that took care of a lot of bipolar patients on the intramural program at NIMH, one to two patients would end up getting hallucinations on a normal dose of Wellbutrin as a function of their sensitivity to their medication.

Another medicine that's used frequently now in pediatrics is Levetiracetam or Keppra, which is used for seizure order. And we get on our in-patient unit at Children's who are on the consult service four to five kids a year who are admitted with hallucinations or other psychotic symptoms such as paranoid delusions as a result of being on Keppra.

They don't have a history of psychiatric illness. They have epilepsy. They have gone on this drug to treat very difficult to treat epilepsy, and sometimes they get psychotic symptoms. It is in the labeling, but, again, with the image forebrain, and with certain types of medication, you can see hallucinations even at normal doses. We're not talking about overdosing when for most people if they took 20 times the normal dose of any of the stimulants they would start to see psychotic symptoms.

I think what I talk to parents about as a clinician is to see if they've had bad reactions in the past to any of these medications, are they more sensitive to side effects. We had one of the children in a trial actually for Atomoxetine who had had bad reactions to several medications, ended up developing hallucinations on Atomoxetine, stopped that drug, end the study -- I'm sure it's in the filing that went to

you guys -- and ended up doing fine on a stimulant.

And so I think part of it is not so much that we need to say these medicines are bad because sometimes they have a scary side effect. But to say yes when you're talking to parents they should know this is a side effect that's possible, so that when it happens they can bring it up to you at the next visit.

But I think -- I think we need to put it in perspective. If you had to ask me what causes the most hallucinations, I would say PCP, which the vets still use and we sometimes use for anesthetic agents. Keppra is number two, and these kinds of medications are much lower than even other medicines like antidepressants when somebody gets manic, and then becomes delusional and thinks that they're the President of the United States and in charge of the world.

So I think it's important to warn people, and I think especially for primary care doctors and pediatricians who don't always get a thorough family history of mental illness, it's a good thing to get, so that when you're starting a kid for ADHD on medicine, since many of these kids can have co-morbid bipolar disorder, you want to be more aware when you're treating them to ask about that and to monitor

them closely. Or if it's a kid who has already had problems on medicines before, to start out at a lower dose and see them frequently.

And the other thing I wanted to bring up was in the NINDS funded study called CAT, which is for methylphenidate clonidine placebo, or the combination, that safety data has been finished. The report has gone to NINDS. I was on the Data Safety Monitoring Committee for that study, and that's going to be presented at the Child Psychiatry Academy meetings in Toronto.

But, in essence, there was no difference in the cardiac outcome in terms of blood pressure, QTC, pulse rate, change in systolic and diastolic blood pressure in the four groups. And I think that's another bit of safety information that will be coming out that will be important for you guys to know.

And that was it. Thank you.

ACTING CHAIR NELSON: Thank you.

So I guess it's time to ask for other comments. Yes? Okay. Feel free to introduce yourself, since I obviously can't.

(Laughter.)

DR. CICCONE: Would you like me to tell you who I am?

(Laughter.)

I'm going to read a prepared statement. I'm Patrick Ciccone. I'm the Vice President of Medical Affairs for McNeil Consumer and Specialty Pharmaceuticals.

As previously indicated, we introduced Concerta in August 2000. Millions of children have benefitted from this once daily 12-hour treatment. As a company, we're committed to providing patients with safe and effective medications that address important medical needs.

Like the FDA, we too are committee to providing patients and prescribing physicians with comprehensive information about our products. As part of the AERS reporting system, it is often the case that adverse effects reports are not submitted directly to the FDA -- rather, are submitted directly to the FDA, rather than to the sponsor.

We look forward to receiving the FDA's entire package of detailed data, and to the opportunity to work with the agency to further evaluate these reports.

Thank you very much.

We have a team of people here who will be very willing to answer any questions, or try to answer

any questions for you.

ACTING CHAIR NELSON: Thank you. So let me ask if there is anyone else who wants to speak during the open public session. Hearing and seeing none, this closes the open public hearing, and we can move, I assume, to Dianne's overview and then to our discussion.

DR. MURPHY: I'm going to do it from here, if it's okay. It's really a statement. Jan, you have the -- okay. Can you hear that? Okay.

I was asked to present this statement, which is really a consensus of the thinking of the people who have been involved in the review of the adverse events with -- on these products within FDA.

The FDA has identified two possible safety concerns with the methylphenidate drug products -- psychiatric adverse events and cardiovascular adverse events. I'm going to address the psychiatric adverse events first.

The post-marketing reports received by FDA regarding Concerta and other methylphenidate products include psychiatric events such as visual hallucinations, suicidal ideations, psychotic behavior, as well as aggression or violent behavior. We intend to make labeling changes describing these

events.

In addition, we believe it is critical to examine the other stimulant products approved for ADHD, specifically the amphetamine products and atomoxetine -- not a stimulant -- to determine if they, too, are associated with these adverse events.

We are currently examining the post-marketing reports for these products. We will bring to this Committee a review of the amphetamine adverse events, and we hope events associated with atomoxetine in early 2006. Given that both methylphenidates and amphetamines are stimulants used in the treatment of ADHD, it is important we evaluate both stimulant classes in order to avoid potential switching from one class to the other based on incomplete safety assessments.

We are seeking your comments on this approach, and, in addition, we are asking you if there is any information that we should provide the public while we are examining these post-marketing reports for the other stimulant products.

Secondly, as is relevant to the cardiovascular adverse events -- in August 2004, the FDA reviewed post-marketing cardiovascular adverse events for all stimulant medications and relabeled

Adderall XR to carry a warning about sudden cardiovascular deaths, especially in children with underlying heart disease.

At this Pediatric Advisory Committee, the FDA has presented post-marketing reports of adverse event -- adverse cardiovascular events with the use of Concerta. Examples of these cardiovascular events include reports of hypertension, syncope, chest pain, prolonged QTC, arrhythimas, and tachycardia.

The agency believes that it is not yet possible to determine whether these events, especially the more serious ones, are causally associated with these treatments, and the FDA is pursuing additional means to better characterize the cardiovascular risk for all drug products approved for ADHD.

Potential options under consideration include population-based pharmacokinetic -- pharmacoepidemiologic studies, long-term safety trials, and other targeted cardiovascular risk studies.

It is our proposal that the FDA obtain these additional data to help guide the development of any regulatory action regarding cardiovascular risk of drug products approved for the treatment of ADHD. We are seeking your comments on this approach, and,

again, your input as to whether there is any information that should be shared with the public while these studies are being conducted.

This is in place of our usual questions, series of questions. We wanted to break them up into those two components for you, and ask you to address them separately if you could.

ACTING CHAIR NELSON: Yes. I was going to suggest that we focus on psychiatric first, and then we can take cardiovascular as a second component. And I might remind members of the Committee, we are certainly free, if we feel we need additional information, to ask questions of anyone who has spoken today at our discretion, including people from the sponsor or Dr. Greenhill or Dr. Robb or members of the FDA.

So why don't we start out a discussion on the psychiatric observed adverse events and the approach that has been proposed by the FDA. Who would like to kick us off? Tom?

DR. NEWMAN: I support the approach. I actually had a question that I didn't get to ask earlier that maybe the sponsors of the drug would be best able to answer. That relates back to when we were talking about pharmacokinetics, and the question

is why the starting dose is the same for a 16-year old and a 17-year -- a 6-year and a 17-year old, the starting dose of 18 milligrams, when we know 6-year olds are a lot smaller?

Why is the starting dose the same? Why not dose assess on a milligram per kilo basis, like we do every other drug in pediatrics? So who would like to tackle that question, if anyone? I don't hear any takers. It was labeled that way. I'd think the FDA at least would take a stab, or is it --

DR. ANDREASON: As far as I know, with Concerta it was labeled -- go ahead. He is --

DR. CICCONE: Well, first of all, I think we're taking the advise of Dr. Rappley in the recommendations we make, which is that you start out with the lowest possible effective dose. So 18 is the standard dose that we recommend, even in the PDR, and we do tell people to try to ratchet up as rapidly as you can as long as you're getting more efficacy and there is no emergent treatment side effects.

DR. NEWMAN: My question would be: if 18 is the right dose to start with for a 17-year old, why would you start with that dose for a 6-year old?

DR. CICCONE: I think traditionally younger people have been treated with these agents,

and the standard, at least in retrospective review of the data for what has turned out to be effective treatment for children, has been one milligram per kilogram. So if you look at it that way, 18 milligrams is not a heck of a lot.

DR. NEWMAN: Except then it's not enough for a big kid.

DR. CICCONE: No. Well, but that's true, and there are many physicians that we know of who do start at higher doses. We haven't recommended that, though.

ACTING CHAIR NELSON: Marsha, do you want to dive in as a clinician practicing in the area?

DR. RAPPLEY: I think that increasingly the research shows us that the higher doses are more effective, and that they are limited by side effects in some children. And so probably our tendency to start at a lower dose is our caution and our tradition with this.

And over the next 10 years we'll probably be starting at higher doses for the older kids, because it looks like 72 milligrams might be the right dose for adolescents. So to start at 18 and work all the way up to 72 may be doing a teenager a disservice. It might take a whole year to make that sort of

determination.

So I -- I think that it has taken studies like the MTA study, the 500 patients that are studied in such a systematic way over time, to make us confident that it's -- it's better to use the higher doses for the more severe symptoms in the older kids.

ACTING CHAIR NELSON: Go ahead. Yes?

DR. CICCONE: I'd like to add something. If you look at the adolescent data, you'll see that even though we started all patients at 18 milligrams, virtually nobody stayed there. I think there were four patients in the entire sample that stayed at 18 milligrams.

Also, if you look at adult data, with TID methylphenidate, what you find out is that on average 70 to 80 milligrams of drug are required to effectively treat ADHD. So that turns out to be one milligram per kilogram as well.

DR. ANDREASON: Maybe to answer your question about milligram per kilogram dosing and why 18 was started, the studies were designed to start at the lowest dose that was available, and that happened to be 18. There were fixed doses, and we did have a concern about smaller children getting 72 milligrams, and, therefore, limited the study to only expose older

and heavier kids to the 72 milligram dose.

Because we were concerned about children getting the lowest effective dose, and limiting the potential adverse events, we supported them in their design to titrate the dose up. But it's a little bit difficult I guess for us to support a labeling that we don't have data on, so the labeling actually says to do what they did in the study.

But your question is -- remains a good one. Is there a better dose to start at for older, bigger kids? And I don't have any information to answer that question.

ACTING CHAIR NELSON: Before going to Michael, let me see if I can focus the question that we're being asked into a couple of sub-questions. You've already stated that it's your intention to make labeling changes.

I think what we heard in Susan's presentation was there is a lot in the label that are in many different places, some of which relates to the adverse events that have been observed, some of which may or may not be the same language, and it may not be packaged in a way that's easily accessible and understandable to both clinicians and to parents, but you haven't necessarily said what that labeling change

is.

So the first question is affirming a labeling change. We're not really being asked that question, but we could certainly discuss that.

But the second, broader question is the interpretation of the data we were presented would lead one to assume this is a class effect, although you are discussing it in the context of a single drug. And so what you're really asking -- you know, one of the issues is if you change the label on one, what happens to the others?

And do you delay the labeling change, which means you're delaying the information you get out to the public through labels, until you complete the review that's not going to happen until sometime next year? Which means there is this uncomfortable period of time where you've got an individual labeling change for what you assume is a class effect, but you haven't generated the data to warrant the class labeling change.

So I guess I would just ask for an affirmation if I've got that right, and if we should then focus primarily on what we should be doing in this sort of lacuna, if you will, between a single labeling change, which I realize may take some time to

actually put into effect, and when we finally get data that would suggest or confirm what would appear to be a reasonable hypothesis that it's a class effect.

DR. MURPHY: I think a lacuna is a nice description of where you have -- you stated it clearly. We think we know what we want to do. Clearly, if the Committee has a comment they would like to make to us, after having read all of this data, we'll be glad to hear it.

Our issue is that we think this is -- involves all the stimulants. We want to finish that analysis. That's going to take us a while. And is there any recommendation the Committee has for us on how to communicate -- because this is a difficult situation -- while we are getting the rest of the data analyzed?

ACTING CHAIR NELSON: I'll go Victor, and then Richard, and I think, Tom, you had your hand up. And Michael.

DR. SANTANA: So I am struggling with this, too, because my concern -- and I think you said it very well in one of your slides -- that changing in -- changing it in one place, and not changing it for the class effect, may lead to a change in practice, and you have not then addressed the safety issue,

which is what we're here to do today.

So the practice may change if you do it in one drug, and you don't do it for the class of drugs, and people will go switch to the other compounds and this issue may still be there. And then, you have not really addressed the safety issue. So that bothers me a lot.

DR. MURPHY: And it could be kids who aren't even having adverse effects.

DR. SANTANA: Right.

DR. MURPHY: So, I mean, that's --

DR. SANTANA: So I don't know how to resolve that, but it bothers me that if we -- if we do a label change for the drug that we're considering today, but we don't have data yet to say that it's a class effect across all these drugs, and ultimately that data does demonstrate that it's a class effect when you do the review, then unfortunately for those patients today you have not resolved the safety issue.

ACTING CHAIR NELSON: Bob, you might want to introduce yourself, since you weren't here this morning.

(Laughter.)

DR. TEMPLE: I'm Bob Temple. I'm the Director of the Office of Drug Evaluation I, which --

in which drugs like this live. Can you comment on how much you think an addition to the labeling of certain of these psychiatric adverse effects say -- ignoring cardiovascular for the moment -- would actually change behavior?

This is not an uncommon problem. You discover something reported for one member of a class. You strongly suspect that it's related to other members of the class, but you don't have any data.

So, you know, how long do you wait? What do you do? You've already heard that there's a plan to get on this other stuff quite quickly, so that's obviously part of it. But one question is: would we be doing damage?

Would people switch because they saw hallucinations listed in the side effects for methylphenidate products but not for the other products? So some sense of how bad it could be I think, which you probably have better than we do, would be helpful.

ACTING CHAIR NELSON: Well, I think it's difficult to say. There's plenty of evidence to suggest people don't pay attention to labeling when they --

(Laughter.)

-- prescribe drugs. So I think it's an unknown question. It's less, I suppose, the labeling change than it is the message that comes out of a meeting such as this.

DR. TEMPLE: Well, you know, a box warning that applied to one member of a class, you would very much expect that might drive people toward another member of the class. But this isn't that, so -- I know it's hard to answer the question. That's why we pay you the big bucks.

(Laughter.)

ACTING CHAIR NELSON: Before I go on to Richard, let me just ask, what are the -- it might be helpful to the committee to have someone review the various mechanisms that the FDA can use to actually communicate. Apart from a meeting like this, you have a number of different mechanisms available to you, so -- besides the label. What are those mechanisms?

DR. MURPHY: I'll start. We have public health advisories, which we put out when we think there is a public health safety issue that we really need to notify people. We have press alerts. We have our -- now we have our drug safety web Drug Watch that we put information up on the web.

And we can work with various

organizations, like the Academy of Pediatrics or Family Practitioners. But, again, you -- when we do that, you want to have a fairly articulate message that you're trying to get out. So have I missed some other mechanisms?

I think that's why we're struggling, not wanting to appear that we're not telling people something, trying to get these messages completely -- or these adverse events completely evaluated, so we have -- we can come out and say they're all the same or they aren't -- you know, one or the other. And how do you communicate in the meantime that -- that message?

So I'm -- we're interested in hearing from you if you have some thoughts of what the message should be and how we should do it.

ACTING CHAIR NELSON: Richard?

DR. GORMAN: I'll give you some anecdotal data on how effective you are. When the Adderall XR label changed, three patients in my practice all -- 100 percent with cardiac structural lesions -- called me before I knew the labeling change was done and asked to be switched to another product.

So with a very specific message in a very small population, that message got out very rapidly,

and behavior changed.

The kind of labeling change we're talking about today, which is maybe a little bit more diffuse, would probably take a lot longer to get out. It can cause hallucinations. But when it gets sudden cardiac death in people with, you know, cardiac -- underlying cardiac disease, that message got out very rapidly.

I went through a data search of my own charts to see if there was anybody in my practice with a cardiovascular structural disease who was on that particular agent who hadn't called me, and the answer was no. They all called me before I got to them. So I think there are specific messages that get out there very rapidly.

I just had one suggestion to the agency as they go forward. If other drugs come up that are going to be labeled for treatment of ADHD, if they don't fall in the classes presently under scrutiny, that they be added to the list of drugs that be put under scrutiny.

So if it's not a stimulant and not Strattera, and not a dexamphetamine salt, but approved for the treatment of ADHD, that they then get put under the same -- so that we don't drive people to yet another class that hasn't been studied.

ACTING CHAIR NELSON: Michael?

DR. FANT: Yes. This is just a followup to the question that Tom was asking earlier, and the last point that was made in that discussion, that in the older kids, you know, perhaps 18 milligrams may be starting too low.

But correct me if I'm wrong, what I've basically heard today is that the younger the kids, you know, the more frequently we see adverse events occur. And so my question is: is 18 milligrams too high of a place to start with the younger kids? And should we be looking at dosing -- you know, starting lower in those kids and working our way up? To see where the efficacy breakpoints are versus the adverse events.

ACTING CHAIR NELSON: Anyone want to take a stab at --

DR. ANDREASON: I'd love to see it. We're always interested in dose-response, especially with attention deficit disorder. And -- oh, okay. I was getting a sign over here.

We like to see dose-response studies in the division. We -- like I said earlier, I think the hardest decision that we have is picking a highest recommended dose, and what we usually try and rely on

are fixed dose studies where we see if there is a differential effect as you increase the dose.

In some studies, we have found that the lowest effective dose studied is as effective as any other dose, leaving us with the question of: what about lower doses? And so, yes, we would love to see studies like that.

Recently, we did see a study where -- and I'm -- I apologize, I'm trying to remember whether it's been approved or approvable. And if it's approvable, I can't be terribly specific. But where the lowest dose tested was half as effective as the next highest dose, but the dose above that was no more effective than that -- it was a 20 milligram dose. Ten was -- gave a response of about six points. Twenty gave a response of about 12 points. And then, 30 and 40 gave responses that were numerically less than the 20 milligram dose.

So our cap was 20 in that study, but we did have good dose information on 10. So we felt like that dose range was adequately explored.

Some of the other studies have not been able to separate efficacy out from the lowest dose, and we would love to see studies like that.

ACTING CHAIR NELSON: Bob?

DR. WARD: I think one of the themes that has come out, both yesterday and today, has to do with accurate ascertainment of the frequency of the adverse effects. And I'm not convinced that the psychiatric reactions of suicidality and psychosis are increased by the medication per se.

They certainly may be, but I -- I think we need a systematic study of the frequency of these relative to the baseline illness as well. We need a good denominator. We need a good numerator with accurate determination in a study powered for safety, and so that we can really have accurate information.

That doesn't come immediately. And to the extent that we feel there is a public health issue to be served, I think that's -- I think we should act, but I think we need to almost reserve the opportunity to revise that action if we find that the medications are not precipitating these events. Instead, that these are events related to the underlying illness rather than to either changes in the medication or to starting a medication.

We may find just the opposite, and if we do then it reinforces it. But it'll take us a while to have that information.

ACTING CHAIR NELSON: Dennis?

DR. BIER: Yes. I would like to I think reaffirm that. I mean, I would have, you know, some -- some debate, you know, among my -- within myself, you know, dealing with the issue of labeling a member of the class -- one member of a class when we were concerned about all the members of the class, if I had what I felt were very good data that that member of the class did something.

Here I'm not sure that we're going to label one member of a class when I'm not sure that the signal, you know, is above the noise. And the reason I am also concerned about that as a physician is even though I don't prescribe these particular drugs, I prescribe a lot of other drugs, which have, you know, long lists of complications.

And parents ask what those lists are, and as a physician you're obliged to explain those to them. And we -- we have parents who live for years worried about complications that are very rare that you -- that there's no evidence, in fact, that they're really causal. And, in addition, the amount of time a physician spends regoing over that time and again when a person is on a drug is substantial.

I think we -- we put, you know, certain kinds of fears in parents' minds that they're already

struggling about whether or not they should use these medications. So I'm less sanguine about, you know, putting things down that I don't feel, you know, strongly are, you know, shown by the data.

ACTING CHAIR NELSON: Let me ask you a question on that, and I'll -- then I'll go to Deborah. On the slide that Dr. Greenhill put up where he showed the universe of ADHD in a trial which had good diagnostics, where then you had an overlap with about half a dozen different conditions, with some kids looking like they had four or three, imagine carrying that into your pediatric practice where the primary manifestation is ADHD. It goes back to this notion that with the stimulant you then uncover these other co-morbidities.

I'm torn, because I agree that I wouldn't ascribe causality in the way we normally do to the drug under those circumstances. But yet, given the difficulty with diagnosis, I would want that information to be available to clinicians and to parents in making decisions, maybe not about starting the drug but about what should they be looking for and reporting back to their clinician and watching for if, in fact, that's what gets manifested.

So, and, you know, often the labeling --

the label is interpreted as causality predominantly. I think that's how people read the label, "The drug causes these things." If you're sophisticated, you look at the confidence intervals like Tom and Judith and things, and recognize that the safety events may or may not.

But that's, I think, the tension in terms of communication versus ascribing causality.

Deborah?

MS. DOKKEN: I have two sort of layperson reactions to this. One is I remember the great respect I had for a college professor who would tell us when he didn't know the answer, but he assured us that he would, you know, make a very concerted effort to get back to us, and I wonder if the FDA can be in that position.

The other comment is I think the train is already out of the station. And for -- for us as a Committee and the FDA to say nothing when The Wall Street Journal and USA Today and everyone else, because many parents, and certainly parents of kids with ADHD, are incredible advocates for their children, and they are on top of all this information.

So they already know that these discussions are taking place. So I -- you know, we

are obliged to say something. And so many times today I -- you know, what we're all troubled about is, what does all this data mean? And many comments about it's not predictable, it's idiosyncratic with, you know, individual patients. That's where empowering parents who see their kids way more than certainly the family physician, but even more than teachers, etcetera -- I mean, empower parents to be the ones who are watching for these, even if they're not going to happen.

If we're worried about safety, then empower parents to have enough information to truly, you know, monitor their own child's safety.

ACTING CHAIR NELSON: Thank you.

Tom, Michael, Marsha, and then Mary.

DR. NEWMAN: Yes, I want to agree with that, and I think just -- I want to emphasize that -- sort of what everybody has been saying, that what -- what the parents and the physicians need is some estimate of the risk, not just a list of these other bad things that can happen. But is it 1 in 100, 1 in 5,000, 1 in 100,000, whatever our best estimate is?

And actually I had -- Dr. Greenhill had estimated 1 in 5,000 for the risk of psychosis, and I just -- I wonder how he was able to get that number, and where that came from, and -- because I think

people are likely to think that it's more common than it is if we just list it and it's in the front page of the newspaper. And I have to say that none of what I've heard today about these medications makes me particularly concerned.

ACTING CHAIR NELSON: Michael?

DR. FANT: Just from an operational standpoint -- this question is to the FDA officials -- is it possible in the wording to convey the message of concern that's been raised, so that patients and families are aware of that concern, without conveying the idea that we truly know what the real answer is?

I mean, we're sort of in a position where, I agree, you know, we -- you know, something needs to be said. But is it possible to convey that kind of -- you know, to have that sort of nuanced wording that brings it to people's attention, but not claiming to know more than we really know?

DR. TRONTELL: I think the agency is struggling how to deal with this twilight zone, where we have a concern but we may not be able to articulate it with certainty, or to articulate it in terms of a numeric risk. And that, in fact, is part of the rationale behind the proposed drug safety information, what's been termed "Drug Watch," where the agency

would put this information forward for the public to be aware, but to indicate within that information that there's limitations.

The term of art I think we've used is "emerging," and we're now in a period of public commentary where we're asking the public to tell us as an agency what they think of our proposal to do that. We want to avoid being paternalistic. We want to share information responsibly.

We recognize when we speak it it may provoke even stronger reactions than we might have -- might have presumed would happen. But how do we do it in such a way that people don't believe we're withholding information while we still have some degree of uncertainty? So we'd appreciate such discussion on that particular proposal or other proposals.

ACTING CHAIR NELSON: Bob?

DR. TEMPLE: There's no question we can put our reservations about data in the labeling, and there are many examples. If you are interested -- apart from giving people early warnings of things we haven't figured out yet, there are some things we may never figure out.

The classic, most difficult case you can

name is where the adverse reaction is associated with the very disease that's being treated, or often associated with it, which is what you have here, which is what you have whenever you have cardiovascular effects that occur with a drug that's being used for a cardiovascular treatment. It's very, very hard.

But a recent example of where this was done is that in the part of antidepressant labeling related to adults, there is a statement that it's not uncommon to see worsening when people are started on therapy. This has been in labeling for a while in one form or another.

It says quite specifically we don't know whether the drugs do that, but that anybody starting someone on therapy ought to pay attention for worsening. There's nothing about this that would not allow us to put something in the labeling and say, "We're not sure whether these events are related to the use of the drug, but they do happen and you should be alert to them." There's no impediment to doing that. And it sounds like I hear a number of people thinking we should be doing something like that.

Then, if you get more data from either large, controlled trials, or an epidemiologic study, you can refine that and say, "Oh, yes, it does it,"

which is sort of what happened with the pediatric component of suicidality, when we got enough data to say something for sure.

ACTING CHAIR NELSON: Michael? Marsha?

DR. RAPPLEY: Well, I agree that if we don't go on record with some kind of statement, this void will be filled by people who may have other agendas or are less knowledgeable. So I think it's really important that people do look for guidance and leadership here for this kind of thing, especially in areas of uncertainty.

I agree completely that it's a class issue, and that we should examine this across a class of medications -- the medications within the class. I think that also applies to the cardiovascular risk, and that maybe -- I'm not sure why we're separating out the psychiatric issues from the cardiovascular in that way, or maybe I just didn't understand that right.

But if we go -- if we seek to gain more information about the risks of prolonged QT syndrome in methylphenidate, that should apply to our dextroamphetamine products and all medications used for ADHD. I agree with that.

Would it be possible to, instead of

revamping the entire label, which is probably eventually what would have to happen for all of these meds, could you insert something at the top that might say, "Please note that you'll find information about possible adverse effects in seven places." I counted as people were talking -- "in seven places on the label.

"And while we are investigating this in a number of medications used for ADHD, please make sure you examine these following areas for information about adverse effects." And then it's all there, and you haven't necessarily sensationalized it, but you've brought people's attention to it.

And then, after we get information about the dextroamphetamine products and the atomoxetine products, it may be that the label itself needs to be reorganized, so that people don't have to look in seven places. Or maybe it's good to have it in seven places, because it's reinforced. I mean, it could go either way about that.

But it seems like guiding people -- one of the issues is where to look, and will it be obvious when we read. And, really, even though I've written a review article that took me 18 months to write, I didn't realize that it would be in so many different

places on the label. I don't think that ever occurred to me, that I should have -- to be thorough, I should have looked in seven places on every label in doing that review.

So I think that kind of guidance for people would be good.

ACTING CHAIR NELSON: Mary, and then Angela, and then Judith.

DR. GLODE: This might be a question either for Dr. Greenhill or Dr. Rappley to just comment on, and that's just the issue of specificity of the potential adverse effects in terms of a specific description. So I worry, again, based on the antidepressant issue, of coding these reactions, perhaps without an open enough mind of what's really happening.

So I was just prompted by that when Dr. Greenhill mentioned in preschool younger children now, and I can't remember whether it was people who stopped the drug or whatever, but it had to do with emotional outbursts. And it just occurred to me that an emotional outburst in a three-year old might take a -- might -- no, might, by description of a sophisticated child psychiatrist, actually be hallucinations or psychosis, but might get coded.

And it went back to the antidepressant of it was coded under emotional liability, but on a retrospective review it was suicidality. So, you know, it's just a plea for a complete description of the side effects, so that when people go back retrospectively they may re-code emotional outburst as psychotic.

DR. DIAZ: And I was just going to emphasize the point that, since the agency has to say something, to say that these concerns have been raised, but that further works need to be done for the entire class, and that it will be expedited, so that people know that the agency is working on these issues, because with all of the data today I'm not even sure that it's just people with ADHD or other kind of diagnosis.

I'm not even sure that the general children and adolescent population do not have this number of things that people just do not report.

ACTING CHAIR NELSON: Judith?

DR. O'FALLON: There are a couple of things. One of them is the conduct of the clinical trials themselves. We've been talking around it a little bit.

Now, obviously, it takes a long time to

make changes in clinical trials methodology, so this isn't going to show up anytime -- I mean, we're looking at years here.

There is the issue of the coding, which has come up so much with respect to the SSRIs and other antidepressants, and now it's -- we see it again here. That's a whole that needs to be addressed, and I expect it's going to take a long time.

But there's another issue nobody has mentioned, really, about this, and that's the exclusions. You know, I've reviewed protocols until they're coming out of my ears, and I know that most clinical trials try to exclude patients who are considered going in to be at particularly high risk.

Well, but then, those patients are treated. They are treated in the real world, and I think there may be -- that the methodology should be looking at these, you know, in terms of admitting them into the trials and following them with appropriate -- characterizing what happens to them appropriately.

So this would be a -- so that when we get done on the other end, we're going to have some information that will be helpful to the actual patient population that's going to be treated.

Now, the other part -- pardon me. What I

keep hearing from the FDA and that we haven't really answered, they say, "What are we supposed to do in the meantime while we're conducting these duties that -- while we're getting this additional information?" Well, I don't think it's going to be in the label. We're looking at the labeling -- the labeling process seems to take a darn long time, as best I can tell.

But the press -- the public press is expressing an interest in some of these issues. And it seems to me that maybe the FDA can engage good press people in a dialogue and a discussion about some of the issues, a nice, frank, informative, non-whatever, not trying to -- just plain trying to explain the -- what they know, what the FDA knows, what they don't know, what more they need to know, why they can't make a real for a while, and what some of the issues are in such a way that the public can be informed, "Okay. This is what we know now; this is what we don't know now. Stay tuned."

I think that's the way to reach the people, not through the labels.

ACTING CHAIR NELSON: If I could follow up on that, and then go to Richard. You echoed the thoughts that I was trying to formulate in my own mind, that -- not that labeling changes take a long

time, but they sort of -- once they do, it's written in stone to some extent.

And whether it would make sense to at least delay a labeling change until one had: a) a good sense of the class effect, and then looking at a labeling change across the class; and then, b) when you've thought though an entire reorganization so that you've eliminated the seven places and you've come down to one place, and the like, might be a reasonable approach.

But then, the question is, well, what to do in the meantime. And in listening to the different approaches, it sounds like maybe the Drug Watch report would be the most productive. It's not clear to me, given the anecdotal intended nature of the data that public health advisory seems appropriate. I mean, that kind of comes out for, you know, things like suicide and antidepressants. But this doesn't seem to be at that level.

And then, if you did a Drug Watch report, just to try and line this out for discussion to try and capture what I've heard, we'd just say, "Well, there are these concerns." We haven't even mentioned the cytogenic concern, but that was the first presentation. But psychiatric issues, the

cardiovascular issues, and then the other ones that were sort of there -- there are these concerns.

Some have already reached a level where likely a labeling change would make sense, but others haven't. Explain that causality is unclear, whether it's the disease or the uncovering of co-morbidities or the drug, at this point is not entirely clear.

And then, ideally, you end up with this balance between, as Dr. Greenhill said, the number needed to treat, number needed to harm, which as I recall in the antidepressant discussion was a very useful sort of way to think about it. That data may not exist right now, but at least try to begin to formulate what that might look like.

So I guess what I'm sort of laying out for discussion is, along with what Judith said, whether a labeling change right now -- sure, that's coming, but a more effective way might be to lay out some of these issues in this lacuna in a Drug Watch report. And then, if we want to get it into the label to at least alert people that don't pay attention to press releases and Drug Watch report, to just say at the top of the label there is a Drug Watch report that pertains to this -- or something.

I mean, whether that can be done

economically. I mean, things are out on the market already, and all of that kind of thing. Separate issue feasibility, but calling people's attention to it, it doesn't strike me that the labeling is where we'd be most effectively communicated, at least in listening.

So I just toss that out there for people to think, as I've listened to the discussion.

I know, Richard, you hand your hand up, if you want to --

DR. GORMAN: I guess I'll follow up on that and then make another comment at the end, which is that this group of medications is in some ways very different and in some ways very similar to a lot of the other ones we use.

These have been remarkably effective, and the people who use them -- the children -- I can only speak to children who are on them, and who show benefit -- their parents are adamant in continuing using them. They may switch around between the particular agents in the class, but they're going to stay in the class if they have been effective, because they're helpful for their children.

And when their children come off the medications, even for a short period of time, the

change in their behavior and performance is noticeable. So the drugs have been used for a long time and very safe from the -- for the people who they are effective for.

And unlike a lot of other drugs that we use, there is a huge public perception that these drugs are potentially dangerous. So parents come into your office saying to you, "Tell me about the side effects." I don't ever get asked about amoxicillin's side effects, and yet I suspect I kill more people than -- not me personally --

(Laughter.)

-- but pediatricians in general -- anaphylaxis from amoxicillin probably results in more deaths than methylphenidate has in the last 15 years in one year. So I suspect there is a perception in the community that these drugs are already questionable in their safety. And if you don't show effectiveness with your dosing rapidly, parents will withdraw their children from the drugs.

So with -- you know, I'm always thinking about, how are we trying to push the pendulum here? And I think by adding a statement in a label or putting out a press release from the Food and Drug Administration in whatever format it takes, that

hallucinations have been reported with methylphenidate products, and it's probably generalizable for the entire class.

However you're going to word that is not going to push the pendulum too far in any direction. It may just bring up the whole arena of concerns about methylphenidates and dexoamphetamines, but it's not going push the pendulum a whole lot. I think the people who think they're safe are going to continue to think they're safe. And I think the people who think that these drugs are really scary are going to continue to think that way.

So I don't think these particular issues -- if you come out with a specific warning as came out with dexamphetamine salts about people with structural cardiac disease, I think that changes peoples' behavior very rapidly. And I think the Food and Drug Administration has -- that's my statement about where I think we need to go with the message.

I think the Food and Drug Administration has an opportunity to cast their safety issues in an entirely different framework, if they can manage to gain the high ground, which is -- I remember when I was young there used to be a poster on my bedroom wall that said, "Sleep tight. Your Air Force is awake."

And --

(Laughter.)

And it was during the time when the bombers were on patrol, and the Soviet missiles were going to rain down on us at any particular moment. So I could sleep, because that poster said my Air Force was awake. And I would be putting that message out. You know, at the Food and Drug Administration, we continue to look at each and every drug on a standardized way to continue to see whether we continue to believe that it's still safe.

And I think that's a message you could put out for Adderall -- I'm sorry, for dexamphetamine salts and methylphenidate that says, you know, we've approved these drugs, but we're still listening to people when they tell us that things go wrong with these drugs. And I think that's a message that would reverberate with the American population and make them feel more comfortable that you are continuing to monitor.

It's not an admission of guilt that you are wrong or you missed something in the clinical trials. It's a statement that we continue to look at that. And when you go back to an issue with -- what I always bring up to my patients who are worried about

vaccines, which is rotavirus vaccine, I bring that right up.

I said, "We don't assume vaccines are safe just because we approve them. We continue to look. If something comes up that's new or different, or the world changes, we change our practice behavior." And I think that would be a message you could send out with this -- with -- not only with this but for all other statements that says, "We are continuing to look. We are not blind to your -- we are listening. We may take a while to act until we have facts, but we are listening to what you have to say and we are concerned about your concerns."

ACTING CHAIR NELSON: Marsha?

DR. RAPPLEY: I think to know -- when you release the information about the liver toxicity with anemoxitine, what mechanism did you use? Because that got out like wildfire, too, but yet it didn't cause panic. People just asked about it. I learned about it. Was that a Drug Watch thing? Or what -- in a press release?

DR. TEMPLE: I'm sure there was a public health advisory, but also a write-in to the labeling, and is it boxed or -- it's a bolded warning. We wanted everybody to know that that was something they

should deal with. There were serious liver injuries.

And as you said, it's enough different from the other available therapies that people continue to find that some people ought to get it.

DR. RAPPLEY: And I didn't mean to imply that it was wrong to have that information in seven areas, because if you -- you need information about overdose -- under/overdose. If a person is worried about overdose, they need to be able to go right to that.

And then, you need the list of adverse events and less than one percent, or however you structure that, you need that there, too. So I think it might be okay for it to be in all different areas. I didn't mean that as dissing that label.

DR. TEMPLE: I should just tell you, coming we hope moderately soon is a change in the structure of labeling to include a piece called highlights, where -- I don't know if this would get into highlights or not, and some attempt to rationalize these various pieces of it.

You'll still find -- you will still find bits -- certain kinds of information in multiple places, because it seems to belong there. And you'll find repetition of information about dosing in the

dosing section and in the warning section, if there's a relation to dose. So it's not going to be perfect in the way you're talking about, but we think it'll be better.

ACTING CHAIR NELSON: Benedetto?

DR. VITIELLO: Just an observation about the possible -- you know, considering the standard of -- the changes in labeling to the class, which seems to be -- at least at this point to be quite premature, because a link has not been found between these events and methylphenidate. Had a link been identified, certainly we needed to consider if there is a class in fact, and to inform other -- also about other drugs that belong to the stimulant class.

But in this particular case, it's narrowly descriptive. So these events have occurred and had been reported during treatment with methylphenidate. No link can be -- no causal link can be established. If anything, one can change the labeling for methylphenidate. I think it's premature to make a decision about the class at this point, it seems to me.

And it seems to me what is being proposed is really, from a practical point of view, probably the only option that is -- because the alternative

will be not to make any changes which also will be sort of awkward, since these reports, after all, have occurred. So what is being proposed seems to me fairly sensible.

ACTING CHAIR NELSON: Let me at this point at least shift to see if there's any other comments that people would make when the focus is on the cardiovascular. My impression of the intent to keep them separate was at least the FDA thought that evidence in favor of the psychiatric was a bit stronger than the cardiovascular, and the approach in the cardiovascular did not include a proposal to change labeling at this point.

What I've heard is a lot of discussion that could apply to both, but I just want to ask -- is there anything special about the cardiovascular, focusing on that, that we should then add? So I'm going to go to Tom, and then Bob.

DR. NEWMAN: Well, I think I wouldn't group all of the psychiatric adverse effects together. I think the evidence for hallucinations was really pretty strong. But that's actually already in the label in the parent education section about hallucinations. So I don't feel a strong need to do that.

I didn't see any kind of an impressive signal for suicidality or suicidal ideation that would make me think that that warrants a Drug Watch or a warning or something new. I mean, this -- these drugs a very, very commonly prescribed, and there were very, very few reports of that. And I just think that's not impressive.

So I think we can within each class -- psychiatric versus cardiovascular -- there are some effects that we know pharmacologically these drugs cause, you know, at overdose, and that if you give -- as people said, if we give people enough of them they will respond that way, and for them I feel comfortable with a causality, and that would be true for the hallucinations.

But I wouldn't group the suicidality in that, and so I'm trying to figure out -- so what should this Drug Watch say? It seems to me that most of these things actually are already in the label, and so I -- I would agree with waiting, considering the drugs as a class. If you are going to do something, do it, you know, for the whole class.

But I guess I don't see the big urgency that there is something new that isn't in the label now that we need to call attention to, because the

things that I've been convinced of are actually already there.

ACTING CHAIR NELSON: Bob?

DR. WARD: You are going to respond to that?

DR. O'FALLON: Yes. It's just that -- yes, it's just that there have been several articles in the newspaper since I left home yesterday morning at 5:00. And so I think there is a -- there is something now that is probably an opportunity now to just, you know, state the -- what's known and what isn't.

ACTING CHAIR NELSON: Yes. I guess, Tom, I would go back to the causalities. It's not clear to me that if there's such an overlap in the phenomenology of these conditions that a warning that may even just be the uncovering of co-morbidity is not appropriate.

So I wouldn't restrict labeling or -- not necessarily labeling but information to the public to simple causality, but to the whole relationship between the use of the drug in a particular condition and how that may impact on parents' understanding, ability to communicate, etcetera.

So I agree with you about the causality

ascription, but I wouldn't limit -- and that's actually some of what I would put into -- if a Drug Watch was appropriate, some of that uncertainty about causality and the undercovering of co-morbidities or -- and the like, which would then come out in this context, which would be very different.

Let me go to Bob, and then over to --

DR. BIER: I would just like to respond to that. I'm not sure that uncovering co-morbidities isn't implying causality. Taking this drug uncovered co-morbidities, and I don't know that these things weren't any different than what's in the general population, irrespective of whether you have ADHD. I just don't see that.

ACTING CHAIR NELSON: Well, the population not having ADHD hopefully isn't getting the drug at all, but --

DR. BIER: To see, you know, three suicides among a million children who don't have ADHD, or -- or conduction disturbances among a million children, these are not things that I see are necessarily uncovering co-morbidities of ADHD.

DR. WARD: Let me make two comments. The first is at least in the lay public that I have contact with, I hear a great deal of disagreement

among parents -- between parents about treating a child or not treating a child, based on what has been in the press and based on these concerns.

And some of the children, by description, sound like they clearly suffer from having untreated ADHD, yet one parent refuses to allow treatment. So we're going to worsen that situation, I fear. I'm not sure we have many alternatives, but -- but I think that that is -- that situation leaves children with a disservice.

Let me turn to the cardiovascular aspect, and I think it is rather different, because, for example, the IKr channel and looking at long QT, we know a great deal more about mechanism of action of that disorder of conduction, and we know a mechanism of action for the drug. And if we didn't have an EKG before that child showed up with long QT to ascribe deriving or developing a long QT syndrome to treatment I think -- I think is already irrational. Okay?

And one case, again, in -- as Dennis said, in a population where we know what the frequency is, I think if it does anything we should simply redouble our efforts to analyze cardiovascular effects before we say anything that would be, again, premature or precipitous, without good data.

ACTING CHAIR NELSON: Elizabeth?

DR. GAROFALO: I just had another question or a thought. I mean, we're doing this BPCA one-year review, and I'm wondering if this would have been approached differently if we didn't have this sort of somewhat arbitrary milestone, not that we can undo it, but would you have -- you know, would these reports have brought -- surfaced this way without this mandatory review?

DR. MURPHY: I think that we can say that the division was already looking at this in some of the more recent studies, particularly the psychiatric. And I thought we separated it because we do feel there is a difference, and was looking at some of these events, so we -- we routinely monitor.

This does provide an opportunity to bring it together. But as we said, it -- we have Adderall coming up. So it's -- we know Adderall is coming up. We just want to make sure that it's clear why we're not doing something in the meantime.

ACTING CHAIR NELSON: Bob?

DR. TEMPLE: I was actually going to make a point something like that. The BPCA forces us to do something that we do all the time anyway, but it also forces us to present it publicly, so that there is a

bunch of material that goes on the website beforehand, and everybody sees things that we might spend a little time considering among ourselves.

So what you're doing here and what you're responding to is going to happen all the time. And, you know, every time -- Anne may want to comment on this. But every time you look at isolated case reports, which don't have any rules about what kind of data people have behind them, it's not like a clinical trial -- there is always going to be the question of whether it's the drug or whether it's the underlying disease.

And in a sense, the public has to learn to cope with that, because it's very hard to interpret reports that aren't obvious. I mean, hepatic necrosis is relatively easy, because it doesn't happen by itself very often. But a lot of other things do happen sometimes. And when you see them at a rate of 1 in 100,000, or 1 in a million, it's the devil to know whether the drug did it or whether it just happened.

And we had to deal with the Adderall case, you know, the Canadian reports, and things like that, in just that way. And they are fundamentally imponderable, so having you help think about what to

do with those kinds of things, and how much reservation to put into the label, and how to go about it, is very helpful. But we're going to see -- we're going to be seeing a lot of these, because BPCA requires it.

ACTING CHAIR NELSON: Dennis, and then Tom.

DR. BIER: You know, the public learning to cope with this obviously is a very complicated issue. And yesterday we heard about, you know, putting consent forms and in eighth -- you know, eighth grade language, the Dietary Guidelines for Americans, because I sat on that committee in the past. It was eighth grade language.

So are we going to have a website which presents how -- this kind of very complicated argument in eighth grade language?

DR. TEMPLE: Probably we don't succeed in doing that. But, you know, we've made a public commitment to put some of our uncertainty onto the website. And our perception is that the public wants that, and that in a certain sense it's fair. Maybe they should know what doubts we have, even if we're not fully satisfied.

Even though -- even there, though, there's

plainly going to be a threshold. You don't put everything on it. And we are learning and listening to people about how to go about doing that. It's a very delicate matter. You know, maybe the public will turn around a year from now and say, "Why are you bothering with this stuff? They don't turn out to be true."

I don't think so, though. I think people would like a chance to see it, and it's our job to put it in a way that tells the data we have, gives our reservations -- I don't -- there's no hesitation about giving reservations about data. And we need to learn to do that in language that does what we want it to do, but we constantly worry about driving people away from useful therapies, for example, by putting a warning. And yet that's not a good excuse for not telling people something, even though you're worried about that. So we have to find a way to do it.

ACTING CHAIR NELSON: Tom?

DR. NEWMAN: Yes. Well, just in response to what you said, I think as long as we include our best estimate of the absolute risk, if it really is 1 in 100,000 or 1 in a million, I think people -- people can cope with that.

I want to come back to what Richard said.

Just because it's -- sort of my perception is the same, which is that these drugs are perceived as more dangerous than many other drugs, and people's baseline level of worry about them is higher than many of the other drugs that are used, and in response to Judith and the USA Today article -- yes, it is in the news already.

The article said that the FDA is considering labeling changes, and it's going to be discussed at this committee meeting. And it could be that the news tomorrow would be the committee looked at the data and were not very impressed, and agreed that more study should be done, but that, you know, this was not really anything very new or very worrisome. And that could, then, be the new story tomorrow.

So I don't think that we have to have the fact that it has been in the press mean that we, therefore, need to issue an alert. We need to look at the data and how strong the signal is and decide based on that.

ACTING CHAIR NELSON: FDA I think is going to offer you a position in their PR office.

(Laughter.)

Richard?

DR. GORMAN: Just in terms of Dr. Temple, you know, I don't think you're going to drive any patient away from this particular therapy. I think you'll make it a little bit more difficult to perhaps initiate the therapy, but people who are on it and its effective -- nobody is going to stop it because there's one more potential warning, contraindication, or adverse event on the label. It's not going to happen.

You may make it a little bit more difficult to start for the clinicians who think it's reasonable. But no one is going to get off this medicine.

ACTING CHAIR NELSON: Marsha?

DR. RAPPLEY: I like a lot of the ideas that have been circulated, and I guess I would, as a clinician, much rather deal with more good information out there, including all of your reservations and our reservations, and have that discussion with my patients and be able to say that I have faith in the FDA. I mean, I say that anyways.

(Laughter.)

But -- and what -- so what we do know, you know, I think we -- we do know some things, and we should put that out there, too. I'd rather be in that

position than have to defend silence or have to have the only source of information be me against a lot of sensational things in the press.

So, and I ask my patients to deal with uncertainty all the time. But maybe I'm a little too Pollyanna about that, but that's just the best way that I have found to work with it.

ACTING CHAIR NELSON: Tom?

DR. NEWMAN: I guess I'm -- so have you heard stuff today that you didn't know before that you wouldn't have guessed from the labeling or the -- or that you think warrants some new kind of warning?

DR. RAPPLEY: No. I don't really see it as a new warning or a new level of alert. It's not like orange or red or whatever.

(Laughter.)

But it's more just responding -- you know, we have this information, and we're processing it. We don't see that this is a -- that this is over what's expected in the general population, but we are continuing to look at it. We're looking at it more broadly. We don't want to be premature in conclusions. This is what we do know. This is what we continue to investigate.

ACTING CHAIR NELSON: Michael?

DR. FANT: Yes. I concur fully with the points that were just made. The way I personally see -- as a citizen see the FDA, and as a member of the committee, in part our role here is one that serves public trust and how to do justice and serve the public trust, both in terms of the individual issues we discussed, but in general terms as well.

And I think it's a lot easier to -- to capture and keep the trust if we communicate information that we think may be important, even if we aren't 100 percent certain, but it's already in the public -- captured the public -- the public's attention, that we address it in some way. It doesn't say how we address it, but I think it needs to be addressed.

And if we're concerned that it may be an issue, we communicate that as best we can. If we aren't sure that it's real, we communicate that as best we can, because I think over the long term the public will -- will deal with that kind of interaction with the agency a lot better than they will deal with silence about things that turn out to be really bad.

And then, does the public trust not hearing about anything -- okay, if I don't hear anything from the FDA, then I can trust there's

nothing to be heard, there's nothing important going on. And so, I mean, I think I hear the concerns about getting too much information and maybe stirring the pot a little bit and stirring up concerns, but I think it -- if it's done carefully and thoughtfully, I think over the long run I think it serves the mission and the interests of the agency and our committee better.

ACTING CHAIR NELSON: I'm beginning to hear a common theme in everyone's comments, so I guess I'd like to ask Dianne, in terms of the questions that we were asked to discuss, have we been concrete enough, or should we be more concrete? I mean, there's been discussions of mechanisms -- a lot of that I think is really up to you and how you can carry that out. So it's not clear we need to be more concrete. But do we need to be more concrete in your judgment?

DR. MURPHY: I don't think so. I think what we've heard is very important, because we've heard that there is no terrible signal, which is what we didn't think we had a signal that was going to warn -- a black box or a unit going out and immediately changing -- we really didn't think that.

We thought that some of this information is in the label. But as Marsha has pointed out, it's

all over the label. Some of it is in one place and not in another, and it may be related to whether you already have a condition or not have a condition. And so our thought was we want to try to make it clearer, you know, what the situation is with the potential adverse events.

And I think I'm -- we're hearing from the committee that our job is to not make it worse and to communicate that we are, you know, continuing to see adverse events. We -- you know, as was presented to you, some of these go away, quite a few of them, when you take children off the product.

And, therefore, we need to be clear with our modification of the dose, and we need to be clear with the public that we're working on not only developing a way of defining this in the label better, or more clearly articulated, which I am not doing very well right now, and also then we have potential other approaches that we're trying to take for the cardiovascular.

And, again, coming back to some of the points that have really been made, we have actually I think stated we don't see -- we can't make any causality. We are very concerned that people not jump to a conclusion on the cardiac that is just because of

one report. We don't want that kind of premature decision being made.

So what we're hearing from you is -- is telling us that we're on the right path. I think that's -- I think that's what I'm hearing.

Paul, do you -- did the committee give you the sort of help you need?

DR. ANDREASON: Yes, I feel like what we're hearing from you is basically what -- what we had thought is that what we have are a series of adverse events that we're fairly familiar with. But that as time has passed, over the lifetime of the drug and over our professional lifetimes, has -- we have learned more about the disease, we have learned more about adverse events that are associated with things like raising blood pressure and pulse over time.

And that as we learn more, we need to update labeling to better describe the things that we already know. For example, I go back to Paul Wender. I remember on rounds with him one day he was doing research on adult attention deficit disorder, and the concept of adults having attention deficit disorder was something that was fairly radical. Adults were supposed to outgrow this.

And he had a set of data that was pretty

good. It showed that adults, at least a good portion of adults, continued to suffer the symptoms. And so at the end of it all, one of the residents said, "So, do you treat your adult patients with stimulants?" And he said, "No. What do you think I want to do, lose my license?"

And it was because the prescribing practices at the time were such that if you treated an adult with a stimulant you came under a fair amount of scrutiny. That has changed a lot. Only recently has a stimulant been approved for the treatment of adult ADHD, and in our review of that we looked seriously at cardiovascular events.

We had to look at post-marketing adverse events and do a -- and have the Office of Drug Safety look at serious cardiovascular risk. And we wanted to make sure that we were appropriately labeling a maximum effective dose, so that we would limit potential long-term cardiovascular risk by limiting as much as possible the amount that the blood pressure would go up. So these are all these types of things.

Now, also, over time the way we look at blood pressure has changed. I remember a time when they said that you don't treat anything that's -- blood pressure that's under 140 over 90. Well, that's

has changed, so we have to pay more attention to the blood pressure effects of medicines that cause increases in blood pressure.

So we have to balance those in labeling, too, and we are more clear on the effects of blood pressure, even when they're not over 140 over 90. So these things are changing as time goes on, and what we wanted to convey was that these are things that we know over time, but perhaps we need to explain them better.

We are not seeing anything that we consider particularly new, but we want to be able to communicate them better.

ACTING CHAIR NELSON: And then, as a followup question, there was a lot of discussion about using a label versus using other devices. Do you feel you want a more concrete sense of the committee as to whether we would suggest using a label is the way to communicate that now for the one product versus delaying that and using other avenues of communication that you have available to you in the meantime before all of the additional data is reviewed and comes up. Do you feel that you need to be any more focused on that question, or you have what you need from us?

DR. MURPHY: I missed the first of it,

Skip, because I was --

ACTING CHAIR NELSON: Well, you have different choices of communication.

DR. MURPHY: Yes.

ACTING CHAIR NELSON: The way this is coming out is you are considering a labeling change, but we've talked about other forms of communication --

DR. MURPHY: Right.

ACTING CHAIR NELSON: -- you could use. So the question is -- my sense of a lot of this discussion is that it was clear if some form of communication should happen now, it's less clear to me that the label is the best way to do that. And I -- do you want anything more concrete other than that sense of our discussion?

DR. MURPHY: I mean, I don't think we need a vote that everybody agrees that we don't need to do a label change right now, because -- unless you think we need it. I heard from the majority -- I think the majority of the committee felt that we need to continue our assessments, and that we should communicate to the public that we, you know, continue to see adverse events.

I think the balance is making sure people understand it's nothing new, but that we are looking,

we continue to see them, and that we will try to make it clearer. Again, coming back to -- I think Marsha said it -- the fact that something may occur with a toxic overdose, someone may not always make the connection that it could occur without a toxic overdose, and we need to make that clearer in the label.

Those are the sort of things that we're talking about, not that there's anything radically new, but that these may occur, not just as a toxic overdose. So I think those are the sort of things, or that we don't know that they are just -- they have occurred in patients who have taken these products, which, as Dr. Temple said, we do when we -- we don't have to make causality links.

So the answer is I don't think we need a vote on that, and I think as far as the communication it -- I'm inferring, from what the committee is saying, we don't need a public health advisory, that we need to find another way of communicating maybe with Drug Watch. I mean, if there's any other specific recommendations, we'd -- you know, I'd be glad to hear them. But right now, I'm hearing that we just need to say something. Is that correct?

ACTING CHAIR NELSON: That's what I've

heard. So that's -- I just wanted to know if you need to hear more.

DR. TEMPLE: Yes. Well, a couple of specific things. I heard most people, not perhaps everybody, say that there's enough known about this now, so that one way or another we have to say something. And we'll think about whether Drug Watch or labeling is best.

And there was not too much worry that adding certain relatively rare things to the adverse reaction section, or wherever it goes, is going to make a major difference in whether people use the drug. To the extent that you actually believe that, that could mean we don't necessarily have to check out the amphetamine ones before we put this in, which is one of the things we have to -- we were trying to think about.

We don't want to divert people away from one therapy to another inappropriately, but maybe that might not have this effect, and we haven't done the analysis of those others yet. So I think the discussion was helpful, and we can try to grapple with all those things. I think that will be all right.

ACTING CHAIR NELSON: Okay. Well, with that clarification, let me go around to the members of

the committee and see if there is other comments. There's no reason, if we've exhausted the question, we have to necessarily stay until 3:30 just for the sake of the clock.

So, but I want to make sure everybody has said what they want to say, and I wanted to make sure that you've heard what you need to hear. So if you have anything else to say -- it looks like Tom, Mike, Marsha, we'll start there, and I'll keep working. I'm assuming that the five of you are satiated in your -- okay. Tom?

DR. NEWMAN: It may just be me hearing myself over and again, but I think that there also was some consensus in the group that we need to have some absolute risk. So just listing that these things occur is not as helpful as your best estimate, with all of its limitations, of what the rate is, even if we don't know what it is but we know that it's less than 1 in 500 or 1,000 or 1 percent.

Just to say we are seeing these adverse effects is not as helpful as a best estimate of the absolute risk. I don't know whether we have consensus on that. Does everyone agree with that, that just listing -- just saying that it occurs is not nearly as helpful as the best estimate of the absolute risk.

ACTING CHAIR NELSON: Bob?

DR. TEMPLE: These are spontaneous reports of things where people make decisions on reporting that we have no idea of. We have enough trouble when it's hepatic necrosis or something. And to try to guess what the reporting rates on these are -- I don't know, Anne may want to comment -- I think would be extraordinarily difficult.

DR. NEWMAN: No. But we have randomized trial data. So we have some things with numerators and denominators to be able to assess these things.

DR. TEMPLE: For those, yes. But those are presumably already in the label, and the ones you are looking at here, the ones that got everybody excited -- hallucinations -- they weren't in there.

DR. NEWMAN: Okay. So then we could say at least that they're this uncommon. Right? We could say that they are less than one percent or whatever it -- we could say based on the randomized trial.

DR. TEMPLE: Perhaps we could say that they weren't seen in clinical trials.

DR. TRONTELL: I mean, I think the suggestion is indirectly that we may be able to cap the risk based upon what we saw or didn't see in clinical trials. And, you know, I think we'll take

that under advisement.

ACTING CHAIR NELSON: And I guess just about -- if there's a non-sponsor-supported, non-submitted trial that's done that you feel is clinically adequate, you can use that data to set those kind of risk estimates? I mean, you know, so there may be information that's outside of the clinical trial submitted for drug approval that might shed some light. Kaiser database was mentioned, for example, other databases over time but not --

DR. TEMPLE: But, again, unless these things get recorded in a hospitalization or something like that, those systems are not so great at that kind of thing. Now, there are practice environments in which people are working to find these things, and maybe one of these days we'll have those data.

But, again, these symptomatic things that then go away are the hardest thing to put numbers on. It's really difficult.

ACTING CHAIR NELSON: So there's a consensus that it's a good thing to have and that it's a hard thing to do.

(Laughter.)

Michael?

DR. FANT: Yes, this is slightly

different, but it's in the spirit of balancing efficacy and safety. And this gets back to my question earlier about -- about the younger kids that may be more sensitive to the adverse -- expressing adverse events than some of the older kids.

And based on what I've heard, it just suggests that, you know, there seems to be a need to restudy those kids, the dose-response of those kids, because if you're dosing them with a dose that's already predisposing them to a higher chance of getting adverse events, they're going to come off the drug and you may be removing some kids from receiving a potential benefit of the drug, or inappropriately exposing them to an elevated risk for toxicity.

That's based on what I've heard today, and throw that out if -- to see if I'm hearing that right or if there is something I'm missing. But based on what I've heard, I really think that there is a need to get a better sense of what we're doing with the younger kids.

ACTING CHAIR NELSON: I'll let the FDA people have the last word as we go around the room. Marsha?

DR. RAPPLEY: That was exactly what I wanted to ask about, too. I heard from Dr. Greenhill

maybe a challenge or a request to reconsider the warning on methylphenidate for children six and under, and I know that is not -- I'm not suggesting we do that in the remaining time, but I think that's very closely related to your comments.

And is there a mechanism to do that? I mean, is there -- because we do now have evidence that we didn't previously have, some of which you presented, and is there a mechanism for the agency to -- to examine that issue? Because I think it's an important one.

ACTING CHAIR NELSON: We'll collect all the questions, and when the -- and let them respond.

Angela? Mary? Victor? Judith?

DR. O'FALLON: Sorry about this laryngitis of mine. You guys, when you do a written request, you basically -- you set the parameters for the studies. And I think it's very important that, you know, you start -- you look carefully at the exclusion criteria, because these exclusions do indeed limit the knowledge coming off the other end.

And this whole past year we've been learning a lot about the inadequacies of coding. And now, we know that these are rare side effects, and yet they might be something -- the psychotic stuff. They

are rare, but they may be very important, or they may be, you know, bad when they occur.

If it's important to get after that, then I think that you -- that we could use the information that we already have in hand to institute a somewhat reasonably standard coding for collecting this kind of data and try to get data so that people -- that we can get at the effect and not have them coded all over the place, so that we don't recognize that there's the same thing being coded several different ways, and, therefore, reducing the frequency counts.

So I think the -- some of their methodology things can be -- the methodology can be shaped up a little bit better for future studies.

ACTING CHAIR NELSON: Deborah? Over to Paul, Dianne, Anne, any further comments? Bob? Susan?

DR. MURPHY: Just that the message I hear is -- and, actually, I think this is a really good question, because we've seen it with some of these other parts. I think we have mentioned this to you before in some of these younger age groups where we're seeing within a very narrow range -- I'm just going to pick three- to eight-year olds.

We're seeing differences in metabolism and

clearance, and all sorts of things, where you -- you actually are seeing one end of that age range where you'll have a decreased clearance, and the other end which you may have an increased clearance. So I think this is a good point, and that we need to look better at that -- pharmacokinetics maybe in that very age group.

But I think that the issue of how we're going to do this, because, you know, it isn't going to be under a written request for these products --

(Laughter.)

-- so -- so for future products, yes. And I think whether we can partner with other entities or groups and try to get some of these questions answered is a good question.

ACTING CHAIR NELSON: Bob?

DR. TEMPLE: Written requests commonly do ask for PK data in all of the pediatric age groups. What's in -- and we also ask that clinical trials include representatives of all of them, too. That sometimes gets waived.

But getting really definitive data on dose-response in each of those groups is not regularly accomplished, let's say. And it's a formidable challenge. We obviously need to think about it; it's

very difficult.

DR. MURPHY: Well, the issue here was the older studies have been done in the younger kids, and so the exclusively was done in the older kids, so that pharmacokinetics is not the area where you needed it, so --

DR. TEMPLE: Right. But it's always hard. Even with the larger samples in adults, I think the dose-response data sometimes leaves something to be desired. You just need massive numbers of people to pin down the differences between neighboring doses. So it's something we worry about a lot, but it's not always easy.

ACTING CHAIR NELSON: Thank you. Well, before we adjourn, I'd just like to say one last word, and that's to think Victor and Mary and Joan, in absentia, who were thanked yesterday by Dianne for their service to the committee. And this is the end of their last meeting on the Pediatric Advisory Committee, and to thank them again for their service.

I'll let Dianne comment on that, and then we'll adjourn.

DR. MURPHY: I'd like to, as always, thank everybody for coming here, for reading your packets that we keep mailing you, 600 pages at a time. I know

it takes a big chunk of your time, and we really appreciate your -- not only your attendance but your careful consideration, your comments. It does help us.

I mean, we -- we think we have a path, and we want to make sure because this is a product that's used in millions of kids. There are lots of opinions about it. And we really do appreciate your -- your discussion today.

Thank you very much.

ACTING CHAIR NELSON: Thank you, and we're adjourned.

(Whereupon, at 3:06 p.m., the proceedings in the foregoing matter were adjourned.)