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by Lynne Peterson

SUMMARY

Two FDA advisory committees met on ADHD drugs in the same week. One determined that the cardiovascular and psychiatric side effects of ADHD drugs are a class effect and do not warrant a black box warning, with the exception of a suicidality warning on Lilly's Strattera. The panel advised the FDA that the labels should all be the same, and a MedGuide should be prepared by the FDA to further inform parents about potential risks and warning signs with the drugs. The other panel determined that Cephalon's Sparlon (modafinil) is effective in ADHD, but they were not convinced it has been shown to be safe. The panel recommended the company be required to conduct a large safety trial before approval.

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FDA-Approved ADHD Drugs Found Beneficial and Safe, but Safety of a New ADHD Drug Questioned

Two FDA advisory committees met recently to discuss the efficacy and safety of drugs to treat attention deficit hyperactivity disorder (ADHD) in children.

- On March 22, 2006, the Pediatric Advisory Committee reviewed all the drugs used for ADHD in children, and concluded that the currently approved drugs do not need additional black box warnings.

- On March 23, 2006, the Psychopharmacologic Drugs Advisory Committee voted unanimously that Cephalon's Sparlon (modafinil), which is sold as Provigil for narcolepsy and some other sleep-related disorders, is effective in ADHD, but they weren't convinced it is safe, recommending the FDA require a large safety trial before approval – and the FDA said that is just what it plans to do.

Pediatric Advisory Committee: ADHD Overview

In a statement at the start of the panel meeting, an FDA official made it clear that the FDA considers ADHD drugs effective and important medications. The FDA's concern is giving physicians, parents, and patients clear risk:benefit information. An FDA official said the goal for this meeting, with respect to ADHD drugs, was for the Pediatric Advisory Committee to:

1. Assess the potential psychiatric and CV risks of products to treat ADHD in children.
2. Advise the FDA on how best to communicate the risk to physicians and parents.
3. Advise the FDA on how best to address the risk for all the therapies used to treat ADHD to avoid inappropriate switching to products for which there is less safety information.

The panel's conclusions were:

1. **No black box.** No new black box is necessary on any of the ADHD drugs. The new labeling that the FDA is introducing for all drugs addresses many of the problems that might otherwise lead to a recommendation for a black box, and panel members were concerned that a black box might frighten parents. The panel chair said, "A black box would scare a number of patients away."

2. **Class effect.** With the exception of suicidality, which appears higher with Lilly's Strattera (atomoxetine), the panel agreed that the cardiovascular and psychiatric side effects are a class effect common to ***all*** ADHD drugs. A panel member said, "If we change the label in one class, people may shift…and I think they are chemically similar. It is hard to justify differential labeling." The FDA

ADHD Drugs

Company	Brand name	Generic name	Approved	Class	Current key warnings
Ovation Pharmaceuticals	Dioxin	methamphetamine	1943	Amphetamine	---
Novartis	Ritalin	methylphenidate	1955	Stimulant (Schedule II)	Agitation
GlaxoSmithKline	Dexedrine	dextroamphetamine	1976	Amphetamine	---
Abbott	Cylert	pemoline	1998	Stimulant	Liver failure Withdrawn from market in May 2005
UCB Pharma	Metadate	methylphenidate	1999	Amphetamine	---
Johnson & Johnson	Concerta	methylphenidate	2000	Stimulant (Schedule II)	Psychosis (abnormal thinking or hallucinations), increased blood pressure, agitation
Shire	Adderall XR	dextroamphetamine	2001	Amphetamine (Schedule II)	Psychosis, drug abuse/dependence, agitation, anxiety, insomnia
Novartis/Celgene	Focalin	dexmethylphenidate	2001	Amphetamine	---
Lilly	Strattera	Atomoxetine	2002	Non-stimulant (Not scheduled)	Suicidal ideation, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, psychomotor restlessness, hypomania, mania
Tyco Healthcare	Methylin	methylphenidate	2002 oral 2003 chewable	Amphetamine	(Chewable not yet marketed)
Cephalon	Sparlon	modafinil	Not approved	Some but not all properties of a stimulant, (Schedule IV)	Not approved for ADHD
Noven Pharmaceuticals	MTS	methylphenidate patch	Not approved	Amphetamine	Not approved for ADHD

disagreed at first, insisting some of the ADHD drugs are pharmacologically quite different. Dr. Thomas Laughren, director of the FDA's new Psychiatry Products Division, said, "I don't think you can throw them all together." Dr. Robert Temple, Director of the FDA's Office of Medical Policy, Center for Drug Research and Evaluation, and also the Director of Drug Evaluation 1 (which is in charge of oncology, neurology, and cardiac drugs), said, "The sort of lumping of all these things is potentially misleading."

However, the panel was adamant that the side effects are a class effect, and the panel appeared to convince the FDA. A panel member said, "We are lumping things together because we don't have enough data to distinguish them…With the current state of information…I think we should consider atomoxetine similar to the others unless it is proven that it isn't.'

3. Label conformity. Labels of the various drugs will be brought into conformance. The FDA began instituting a new label style on January 1, 2006, but the ADHD manufacturers will not be required to move to the new format immediately. Dr. Temple noted, "They might find it attractive, but they are not required (to do that) until it is their turn. We hope it will be a format that is so attractive that people will want to do it."

4. MedGuide. The FDA should do a MedGuide for ADHD drugs, even though the track record indicates MedGuides are difficult to get distributed.

5. CV risk. Doctors and patients should be advised not to give ADHD drugs to children with a pre-existing cardiac condition. A panel member said, "It is pretty clear that there is an increase in blood pressure and heart rate." Another panel member referred to a recent editorial in the ***New England Journal of Medicine*** by Dr. Steve Nissen (president of the American College of Cardiology) that raised questions about the cardiac safety of ADHD drugs, "I think his focus and concern is the over 50 age group, which doesn't apply to us." A cardiologist on the panel said, "(The problem) doesn't rise to the level of a contraindication…I can't recommend doing screening EKGs and echos in everyone going on these medications. That is probably not a cost-effective way to go about this…but measuring blood pressure, etc., would be good, and then having a discussion with the parents about potential cardiovascular symptoms – e.g., shortness of breath, chest pain complaints, etc., especially if the symptoms occur with activity or exercise."

Dr. Temple said, "We (the FDA) still have to come to grips with some recommendations made at the drug safety meeting a month and a half ago, but that pertains mostly to adults, especially with respect to cardiovascular risks…The committee today was not impressed with general cardiovascular risks for children except for children with underlying heart disease."

The panel chair compared the rare incidence of unknown cardiac side effects with ADHD drugs to the sudden cardiac death that can occur with athletes. He said, "We can't just require that many tests…The number of undiagnosed cardiac problems are just too small."

6. Psychosis/mania. There are mechanistic reasons to believe there may be a relationship between the ADHD drugs and rare psychiatric problems, and this should be in the label, but not as a black box. Panel member comments included:

- "I'm concerned some of the events are not what I would characterize as psychosis…There is a range of childhood behavior and experiences that can look like a psychosis or can be self-limiting hallucinations…I'd be happy using hallucinations rather than giving a psychiatric diagnosis."
- "We are throwing around the term psychosis very loosely …Children can have hallucinations without a psychosis."
- "No one is denying SSRIs reduce depression but some patients also become suicidal…I think (ADHD drugs are) a good comparison to SSRIs…Part of the reason the data in SSRIs are so concerning is that the efficacy is really quite weak…That is very different from here."

7. Aggression. Physicians and parents should be warned to be alert for the signs and symptoms of treatment-emergent aggression, but it should be made clear that ADHD drugs also are useful in treating aggression.

8. Suicidality. The panel was not convinced that the suicide risk is increased with ADHD drugs. Dr. Temple said, "Strattera already has a black box for suicidality. The committee was not particularly impressed by the suicidality data from the current analysis. Strattera again emerged to have signal, as did modafinil, but not the other drugs…The reports are difficult to evaluate. CDC surveys high school students every couple of years, 1 in 20 have suicide ideation, and 10% of those make some attempt, but right now, there is not a clear signal of suicidality for the other drugs."

9. Long-term studies. Additional long-term data on ADHD drugs would be useful but is not mandatory. Dr. Laughren said, "(The panel) endorsed the idea that the FDA is exploring the possibility of doing an observational study…They also endorsed a study basically to look closely at patients treated with these drugs for a period of time and doing a careful measure of cardiac function or structure, such as ventricular wall thickens, to see if there are any longer-term risks of taking these drugs."

THE FDA PRESENTATION

Dr. Ben Vitiello of the National Institute of Mental Health (NIMH) discussed the efficacy of the pharmacologic treatment of ADHD. He said the efficacy of stimulants (amphetamines and methylphenidates) in ADHD has been well-documented in numerous studies, both in the short-term and in the long-term (chronic use). He said there is "strong evidence" that pharmacotherapy of ADHD is effective on the symptoms of hyperactivity, impulsiveness, inattention, defiance, aggression, and interpersonal interactions. What isn't known, he said, is whether treatment affects the natural history of ADHD or whether treatment modifies the distal negative outcomes of ADHD (i.e., academic, occupational, and social under-achievement; higher rate of accidents; higher medical costs).

Dr. Paul Andreason, Acting Deputy Director of the FDA's Division of Psychiatry Products, CDER, told the panel that there are differences in where the warnings are placed on ADHD drugs, and he said there are differences in the content of the warning. In January 2006, the FDA proposed a warning label update for methylphenidates and amphetamines that said ADHD drugs could be used with caution in patients with hypertension, CV disease, or cardiac arrhythmia, and modest increase in pulse and blood pressure has been noted.

> *Sudden death has been reported in association with CNS stimulant treatment at usual doses in children with structural cardiac abnormalities. Although some structural cardiac abnormalities alone may carry an increased risk of sudden death, stimulant products generally should not be used in children, adolescents, or adults with known structural cardiac abnormalities.*

Dr. Andrew Mosholder of the FDA's Division of Drug Risk Evaluation, provided some recent epidemiologic data on ADHD:

- A CDC telephone survey conducted in 2003-2004 of ~100,000 children aged 4-17, found:
  - 4.3% of children aged 4-17 received medication for ADHD.
  - Medication use peaks about ages 9-12 – with 9.3% of boys aged 12, and 3.7% of girls aged 11, getting an ADHD drug.
- About one-third of all prescriptions in 2005 were for adults.
- There is a seasonal variation for pediatric use, with the nadir during the summer, but this variation is not seen in adults.

ADHD Drug Usage Trends

Drug	11/2002 - 10/2003 market share	11/2003 - 10/2004 market share	11/2004 - 10/2005 market share	Share of retail prescriptions from 1/2005 - 6/2005
Lilly's Strattera	~8%	~15%	~14%	16.4%
Methylphenidate	~35%	~32%	~34%	48.4%
Amphetamine/ dextroamphetamine	~45%	~40%	~40%	34.9%
Shire's Adderall XR	~61%	~65% (7.3 million prescriptions)	~69% (8.6 million prescriptions)	N/A
Cephalon's Sparlon	N/A	N/A	N/A	0.2%
Pemoline	N/A	N/A	N/A	0.1%

- Psychiatrists write the most ADHD prescriptions (32%), with GPs writing 16%, pediatricians 29%, neurology 5%, internal medicine 4%, and others 14%.
- Currently, ~1 million prescriptions are dispensed monthly for adults, with double that amount written for children.

Cardiovascular (CV) Safety

Dr. David Graham of the FDA's Epidemiology Contracts Study Team commented, "These drugs probably do increase CV risk, but the question is how much. The distinction between a stimulant and a non-stimulant is immaterial to CV risk. All drugs increase norepinephrine levels in a synapse…and increased adrenergic tone is associated with arrhythmias and sudden cardiac death. We think all three of these drugs should be considered to have the same risk…The number of pediatric arrhythmia cases seems surprisingly high."

CV Risks with ADHD Drugs

Drug	Estimated SCD risk ratio	AMI risk ratio	Cerebrovascular accident risk ratio
Background rate in general population	1-9	1-20	3
Lilly's Strattera	10	3-10	10
Methylphenidate	4-5	2-5	4-5
Amphetamine/ dextroamphetamine	4-5	2-5	4-5

ADHD Drug CV Safety

Drug	CV sudden death age ≤18 (rate per 100,000 patient-years)	CV sudden death age ≤16 (rate per 100,000 patient-years)	Non-fatal CV serious adverse events (1999-2003)
Lilly's Strattera	0.2 (3 patients)	1.5 (4 patients)	Yes, currently under review
Methylphenidate	0.2 (11 patients) *	0.2 (2 patients)	8 reports
Amphetamine/ dextroamphetamine	0.3 (13 patients)	0.7 (4 patients)	18 reports
Shire's Adderall XR	(14 patients)	(14 patients)	N/A

* Ritalin in 7 cases and Concerta in 4 cases.

Psychiatric Safety

Dr. Mosholder said the FDA asked sponsors for adverse events from post-marketing and clinical trials since January 1, 2005. The FDA review of these data concluded:

- The frequency of aggression events is higher with MTS, Ritalin LA, and Strattera than with placebo.
- There is little evidence in double-blind trials that these agents reduced events (Sparlon is the only drug with a numerically lower rate vs. placebo).
- The frequency of suicidal events is higher with Sparlon and Strattera than placebo, and the rate for Strattera is statistically significant in the sponsors' analysis.

ADHD Drug Psychiatric Safety

Drug	Psychosis/mania	Aggression or violent behavior	Suicidality
Demographics	No risk factors identified but large proportion involve young children	No identifiable risk factors	Children and adolescents, more male
Conclusions	May not be a rare occurrence, includes hallucinations often described as insect, snakes, or worms (visual and tactile)	Most cases non-serious, but ~20% life-threatening or require hospitalization	Possible causal association cannot be ruled out for amphetamines and methylphenidates
Labeling issues	Labeling does not clearly address risk in patients without identifiable risk factors and does not recommend stopping therapy in patients who develop symptoms	Strattera but not amphetamines as warning	No label for amphetamines and methylphenidates. Strattera has a boxed warning.

Psychiatric Safety of ADHD Drugs

Generic name	Products	Patients in randomized clinical trials	Person years of exposure	Psychosis/mania events per 100 patient-years	Suicidal events per 100 patient-years	Aggression events per 100 patient-years
Methylphenidates	Concerta, Metadate CD, Ritalin LA	~1,200	12.7 Concerta 19.1 Metadate CD 25.7 Ritalin LA	2.8 (3 patients)	0	4.7 (5 patients)
Atomoxetine	Strattera	~1,900	524.6	0.8 (4 patients)	1.5 (6 patients)	8.6 (45 patients)
Dextroamphetamine	Adderall XR	~1,000	63.8	0	1.6 (1 patient)	28.2 (16 patients)
Dexmethylphenidate	Focalin and Focalin XR	~400	49.7	N/A	N/A	N/A
Methylphenidate patch	MTS	~500	30.3	13.2 (4 patients)	0	19.8 (6 patients)
Modafinil	Sparlon/Provigil	~600	75.1	2.7 (2 patients)	5.3 (4 patients)	12.0 (9 patients)
Placebo	---	3,990	425.11	0	0.9	7.1

- Psychosis/mania events are only observed with active drug treatments in double-blind trials, but are observed with all compounds in open-label treatment.

Dr. Kate Gelperin of the FDA's Office of Drug Safety, Division of Drug Risk Evaluation, said she was "a little surprised that a striking majority of (ADHD) cases reported no prior history of violent behavior or aggression." On suicidality, she said, "Suicidality has been identified as a potential safety issue for atomoxetine, but a causal association between other drug therapies cannot be ruled out."

PUBLIC WITNESSES

Forty-one people spoke during the public witness session, and they were fairly evenly divided on the positive and negative aspects of ADHD drugs. The panel chair summed up the responses: "The diversity of the comments impresses me, given the controversy and ongoing complexity of the diagnosis of ADHD…but, more importantly, I expect the willingness of those who testified about their own experience to take us from statistics to the reality – whether those were helped or hurt (by the medication)."

Pro comments included:

- *American Psychiatric Association trustee:* "No one medication works for all children or adults…Appropriate intervention for ADHD saves lives. Specifically, treatment reduces the risk of serious accidents…Research also demonstrates that treatment significantly reduces the risk of substance abuse in adolescents….I fully support the call for more research...updated labeling language…and the development of MedGuides and fact sheets. Physicians and patients need and deserve as much information as possible…(But) I urge you to present any information about potential risks in a balanced context with the appropriate information about efficacy."
- *Parent of daughter with ADHD:* "It is extremely difficult to raise a child with ADHD…Without stimulant therapy, I can't imagine how much more difficult this would be. All parents would prefer not to use medication…and many are terrified to do so…I don't believe the information available to us today justifies a black box warning and doing so will certainly make parents much more fearful. I would urge you to reconsider the black box warning."
- *29-year-old with ADHD who had ADHD as a child:* "My parents tried the natural way, but they finally found we had to turn to medication."
- *American Psychiatric Association #2:* "ADHD is real, highly prevalent, and consistently found to affect up to 7% of school age children and up to 4% of adults…It can serve as a precursor to substance use disorders…(But) any potential pharmacologic treatment must be prescribed judiciously."
- *American Academy of Pediatrics (AAP):* "ADHD is a real disease that causes significant impairment in many children and adults. A careful and accurate diagnosis should be made prior to starting stimulant medication… AAP has developed diagnostic and treatment guidelines…We urge the FDA to pursue further study to see if stimulants cause cardiovascular problems….One way to do that would be through a national registry. We agree it would be prudent to revise the labels to alert clinicians of the possible cardiac side effects…and it should be consistent across all stimulant medications. Rather than a black box, I recommend manufacturers send a letter to physicians."
- "We've been told ADHD doesn't exist…but I've seen it... My granddaughter Jessica didn't ask for it."
- *NIMH researcher and author:* "These are among the most safe and effective medications we know."

Con comments included:

- *Civil rights attorney:* "Parents have been sold a bill of goods on ADHD drugs."
- *Psychiatrist:* "It is time for us to take more responsibility for our children…We need to teach them, to discipline them, and stop foisting the problem of the mythical ADHD. We need to retake our kids."
- "One in five children today is on some ADHD medication. Clearly something is wrong."
- *Psychiatrist who consults to the Virginia State Police:* "I question the validity of ADHD…The assumption of a disease or handicap is erroneous and may make a child worse…No psychological or physical test to diagnose ADHD exists."
- *School psychologist:* "My son and nephew became a victim of Adderall…My son complained of chest pains, and the doctor ignored me…My son lost 19% of his body weight and developed a rash before they changed his medication…I strongly believe there should be a black box warning…I've talked to countless parents who told me their children were (negatively) affected by the medication…I also recommend further research be done …and mandatory not just voluntary reporting."
- "ADHD is a dubious diagnosis…Treatment efficacy is unproven…A meta-analysis of all ADHD studies worldwide found no evidence demonstrating clinical efficacy… In children, bipolar disorder is now common but only in the U.S.…Many of these young bipolar patients have been treated with stimulants or antidepressants."
- "We are sending our kids a mixed message. First we proclaim, 'Just say no to drugs,' and then we give them Ritalin, which is 'speed' on the street."

- "The polypharmacy we are seeing is unregulated…I think we should have mandatory restrictions on access to these drugs, a mandatory registry for doctors who prescribe them, and a contraindication of psychoactive drug cocktails…and limited promotion (no advertising) …Does anyone remember Joe Camel (comparing ADHD drug advertising to past tobacco industry advertising)."
- *Retired teacher:* "A teacher identified my grandson as ADHD, and a psychiatrist prescribed first Mellaril (Novartis, thioridazine) and then Ritalin and Cylert… And he became bipolar…An exuberant six-year-old became a shuffling, academically failing, chemically lobotomized mental patient who believes his brain is broken and he can't live without Ritalin…Remember this started with a teacher's diagnosis."
- "We can't stop with a black box because at the end of the day, there will be a team trying to mitigate it…We need to find a warning that keeps on warning no matter what they do with it on Madison Avenue…I would combine the black box with a RiskMAP program."
- *The mother of 15-year-old Leanne Bessner, who committed suicide shortly after starting Concerta:* "Imagine this is your son or daughter…Imagine discovering that the FDA had hearings (about the safety of ADHD drugs) three months before Concerta was prescribed to your daughter…You (FDA) had the power to save our daughter's life last June, but you did nothing."
- "Schools are the pipeline for an ADHD diagnosis, and I recommend the FDA, perhaps in cooperation with the Department of Education, provide real risk information to each parent."

THE MANUFACTURERS' PERSPECTIVE

There were only three very brief presentations by any of the ADHD drug companies:

➢ **NOVARTIS.** A Novartis official spoke during the public session, defending Ritalin and trying to distance it from any problems that other agents may have. He said, "Ritalin...has a long record of safety and efficacy...for more than 50 years. Ritalin has helped people…There may be differences in the adverse event profiles of these agents."

➢ **LILLY.** A Lilly official emphasized that Strattera is generally safe and effective – and Lilly is committed to continued study of the drug's benefits and risks and to appropriate labeling.

➢ **JOHNSON & JOHNSON.** Two J&J officials defended the safety of Concerta, presenting data from pooled analyses of clinical trials and open-label studies. One argued that the suicide rate with Concerta is even lower than what would be expected in the general population.

Concerta Safety

Measurement	Concerta in open-label studies n=2,825	Concerta in double-blind clinical trials n=321	Placebo in double-blind clinical trials n=318
Sudden death	0	0	0
MI	0	0	0
Stroke	0	0	0
Hypertension	20 (14.3 per 1,000 person-years)	1	0
Aggression and violent behavior	53 per 1,000 person-years (vs. 37.9 placebo)	0	0
Suicide deaths	0	0	0
Suicide ideation	5 (3.6 per 1,000 person-years)	---	---
Suicide attempts	2 (1.4 per 1,000 person-years)	---	---

PANEL DISCUSSION AND QUESTIONS FOR THE PANEL

The key discussion points for the advisory committee – and comments about these by panel members and FDA officials – were:

Psychosis:

- *The FDA's Dr. Laughren:* "I thought the most compelling data on psychosis was from controlled trials…where psychosis occurred across all the programs pretty much… at least across the amphetamines, methylphenidate, and atomoxetine…and there was none in placebo."
- "There were hints to me in the data that what one person might call psychosis, another person might not call psychosis."
- "I think it could be worded: Hallucinatory and perhaps psychotic behavior."
- "We shouldn't be too overly precise about what they (psychiatric events) are."
- "There is a plausible mechanism (to explain psychiatric side effects with ADHD drugs)."

Chair summary: "We heard this could be a class effect…At least, there is plausibility in terms of mechanisms of action for a class effect."

Aggression:

- A panel member compared ADHD drugs to SSRIs for depression, which have been shown to have weak efficacy data and a risk of suicidality. In contrast, he said, the data on ADHD drugs show a substantial benefit. While many children have their aggression reduced with ADHD drugs, there is a group of children in whom the aggression worsens with these drugs.

- *The FDA's Dr. Laughren:* "With psychosis, there were no events with placebo, but there are aggression events in placebo…It is a much different signal than for psychosis."
- *Chair:* "These drugs can both treat aggression and cause it."
- *The FDA's Dr. Temple:* "What I hear is you would put a lighter weight on this but would remind people it is a possibility…I don't think anyone would say this is a reason not to use the drugs – just that when you are telling people what to watch for, this is a weaker signal, but it might be something you should tell people. It is a possibility; it can happen to some people."
- "We want to communicate to the public and to physicians that there is a need for patients and families to sit down and discuss that this is a distinct possibility and may or may not be related to the medication."

Suicidality:

- *Biostatistician:* "We have to put them (all the ADHD drugs) together. If we change label in one class, people may shift, and I think they are chemically similar…It is hard to justify differential labeling."
- *The FDA's Dr. Laughren:* "It may be that Strattera patients were not prescreened and methylphenidate patients were prescreened…(But) we are not seeing a signal from any drug other than atomoxetine, and that is already labeled (with a black box warning), and we are sort of seeing a signal for modafinil…I'm not comfortable extrapolating findings for two programs to the others… We think they are pharmacologically quite different…The action at neuron is quite different…I don't think you can throw them all together."
- *Chair:* There is evidence that there are more instances on one product (an obvious reference to Strattera) in a year than on all the other drugs together…I don't hear enthusiasm for lumping suicidality in with the other indications (as a class effect)."

Cardiovascular risk:

- "It's pretty clear that there is an increase in blood pressure and heart rate."
- *Chair:* "Dr. Steven Nissen (president of the American College of Cardiology) wrote an editorial in the ***New England Journal of Medicine*** on cardiovascular risk (of ADHD drugs)…but I think his focus and concern is the over 50 age group, which doesn't apply to us…If a black box is appropriate for that group but not for (pediatrics) is that something easy (for the FDA) to do?"
- *The FDA's Dr. Temple:* "If we thought there was a need for a black box for adults and not children, it would say that."
- "I can't recommend doing screening EKGs and echos in everyone going on these medications. That is probably not a cost-effective way to go about this."
- *Chair:* "I think it is akin to the athlete (who dies of sudden cardiac death)…We just can't require that many tests...and the number of undiagnosed cardiac problems are just too small."
- *On what to do with atomoxetine, which is the only ADHD drug without a warning about use in children with structural cardiac defects:*
  - "I think it should be a level field."
  - *The FDA's Dr. Temple:* "I think sort of lumping of all these things is potentially misleading."
  - "We are lumping things together because we don't have enough data to distinguish them…I think we should consider atomoxetine similar to the others unless it is proven that it isn't."

Communicating risks:

- *The FDA's Dr. Laughren:* "Generally, with psychiatric drugs…when something is really serious, ***where we are very concerned about causality***, we put it in a black box."
- *Infectious disease specialist:* "In the vaccine world… people have tried to make a better partnership between parents, children, and providers, and they've gone to information sheets, which have been developed mostly by CDC…I don't think parents – or even physicians – read package inserts…I think information sheets might be more helpful…Parents have to read and sign them."
- "A MedGuide would be helpful. The label is the informed consent for the physician…but if there is something you think they should know, something that will change decisions to put someone on a medication...it should be in a MedGuide." However, FDA officials said the FDA has found it difficult to get MedGuides distributed.
- *Chair:* "My impression is: (1) There was a suggestion of a registry, though I've heard the FDA's experience with a registry is not good; (2) Signed consents; (3) The FDA would like to do epidemiological studies, but the budget isn't there…and maybe it would help if we went on record for that…We also need long-term studies. Clinical trials don't get rare events."
- *FDA official:* "We hear you want: a MedGuide, information that will inform people, no black box, aggression that is treatment-emergent as a (side effect to watch), and that all the side effects are a class effect except suicidality."

THE QUESTIONS

The FDA asked the panel the same set of three questions twice – first about psychotic events and then about cardiovascular events with ADHD drugs. There were no up and down votes on any of these, just discussions that led to a consensus. The FDA's Dr. Temple said, "The panel was very helpful...They answered all our questions on children, but we still have some work to do on adults...They are recommendations (for children), but I think we found them pretty good and are likely to follow them." The FDA's Dr. Laughren added, "I heard that the committee reaffirmed the fact that ADHD is not a trivial disease and basically endorsed its importance and disability…and they said that this class of drugs has a very substantial benefit in this population."

QUESTION 1. What are the important messages you think should be conveyed to physicians and parents regarding these potential risks? Please comment on the strength of the evidence relevant to the identified risks. As appropriate identify differences among drug products.

QUESTION 2. Are the messages about these potential risks being adequately communicated through current labeling? If not, what additional information or changes should be made to the label?

QUESTION 3. What other mechanisms should be employed to communicate these potential risks to practitioners, families, and patients?

OTHER PANEL ACTIONS

Before tackling the risk:benefit equation for ADHD drugs, the Pediatric Advisory Committee made recommendations about three other drugs:

ABBOTT'S Meridia (sibutramine), a weight loss medication. The label for this drug warns of increased blood pressure in some patients, but concerns about CV risks and fetal toxicity have also been raised. From November 1997 through August 2003, there were 54 deaths (30 due to CV disease) and 224 serious non-fatal CV events in the U.S. in patients on Meridia. An FDA reviewer said event reports appear to spike in conjunction with publicity and personal injury attorney marketing. The FDA denied a Public Citizen petition to remove Meridia from the market, but he said Abbott has been pro-active in educating doctors about appropriate use, adding, "Clearly, patients with a history of CV events should not be taking the drug." He also said the FDA believes the pregnancy risk is adequately defined with current labeling, "We feel Meridia's current Pregnancy Category C status is appropriate and does not need to be changed." The ~five-year, 9,000-patient SCOUT trial is underway and, if completed, is likely to answer questions about the CV safety of Meridia.

As a result of post-exclusivity studies, the FDA concluded the efficacy of Meridia in adolescents who are obese has not been adequately studied and the data are inadequate to recommend the use of Meridia in pediatric patients. **The FDA is proposing an additional year of pediatric monitoring and wants to know if the Advisory Committee agrees.**
Unanimously YES

GENZYME'S Clolar (clofarabine), for relapsed or refractory acute lymphoblastic leukemia (ALL). Genzyme estimates that only 200-300 children a year will get Clolar. An FDA reviewer concluded that post-exclusivity adverse events generally were labeled events or would not be unexpected in association with the disease or with the concomitant treatments received by the patients. **The FDA is recommending routine monitoring of Clolar for adverse events in all populations and wants to know if the Pediatric Advisory Committee agrees.**
Unanimously YES

SANOFI-AVENTIS'S Avapro (irbesartan), an anti-hypertensive. The drug is not approved for pediatric use, but ~3,000-4,000 pediatric prescriptions are written annually (0.1% of total prescriptions). During the post-pediatric exclusivity period, the FDA found no concerning safety signals. **The FDA is recommending routine monitoring of irbesartan for adverse events in all populations and wants to know if the Advisory Committee concurs.**
Unanimously YES

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE (PDAC): CEPHALON'S SPARLON (MODAFINIL) NOT SAFE

Modafinil (under the brand name Provigil) was initially approved in 1998 to treat narcolepsy, and it later gained indications to treat obstructive sleep apnea and shift work sleep disorder (SWSD), and Cephalon is seeking a new indication – and a new name, Sparlon – for the treatment of ADHD in children. If and when Sparlon is approved by the FDA, it would be co-promoted by Johnson & Johnson. However, that is not likely to happen soon. The advisory committee voted unanimously that Sparlon is effective in ADHD, but it also voted overwhelmingly that it is ***not*** acceptably safe.

The concern was skin rashes, particularly Stevens Johnson Syndrome (SJS), a severe hypersensitivity reaction which usually involves the skin and the mucous membranes. SJS is serious, is usually treated in a burn unit or intensive care unit (ICU), and has a mortality rate of 3%-15%. The FDA medical reviewer for Sparlon estimated that if modafinil got a 10% market share, there would be 25-488 deaths (0.2%-1.3%), which labeling may not help avoid.

Initially, the panel appeared to be leaning toward simply putting a black box warning on modafinil, but then Dr. Robert Temple, Director of the FDA's Office of Medical Policy, CDER, and also the Director of Drug Evaluation 1, told the

panel that modafinil will definitely get a black box – and it might even get a second-line indication regardless of what the panel did – if it were even approved without additional data, which Dr. Temple appeared to want before approval. Dr. Temple said, "We are seeing a rate of 1 in about 1,000 people, or perhaps 1 in 700-800…It (modafinil) at least gets a black box…1 in 1,000 of a life-threatening event. Everyone has to know about this…And we don't know the rate…I'm virtually certain we would do that (black box)…But it should be in some form or other not recommended as first-line, and we also want to know if we need more data before we say yes."

After those comments, the tone of the panel changed sharply, and all but one member wound up recommending modafinil's safety had to be better established before approval. The panel chair offered these comments after the vote: "There is a lesson here about the need for better assessment of these dermatologic adverse events. I think a lot of these issues would have been settled and the outcome different if we had better documentation that let our dermatology colleagues make better conclusions…So, partly, we are dealing with some fuzzy information…This was not a compelling enough story both on efficacy and safety to reach a comfort level in which this committee could endorse this compound moving forward…So, we erred on the side of consumer protection, and I hope sincerely that the company finds the means to get the additional safety data and that the outcome could be different under those circumstances."

The advisory committee's recommendation – which the FDA afterward indicated will be a requirement – is for either:

1. **Safety trial.** A 3,000-patient, open-label, single-arm safety trial of probably 4-6 weeks that shows ZERO cases of possible or probable SJS. If there are no cases of SJS in 3,000 patients, it would indicate that the SJS rate is "no greater than 1 in 1,000." It would not say anything more than that.

How long would a trial like this take? The panel chair thought it could be done in a year, and the FDA's Dr. Temple said, "There is a lot of disease, so it shouldn't take too long." Before the panel meeting (i.e., in the first approvable letter), the FDA did not request a larger trial, Dr. Temple said.

If there is a single case of SJS, Cephalon has "a real problem," another FDA official said. But there is still an out for Cephalon – option No. 2.

2. **Superiority trial.** A head-to-head trial in patients refractory to another major ADHD drug, with the trial powered to show superiority, not equivalence, of modafinil. I don't know how large this would have to be, but I suspect quite large; that is a statistician issue. Dr. Temple said, "As a last resort drug, 1:1,000 SJS might be okay...If they find one case, then there is a problem. That would be unacceptable... You know reasonably well that if you get SJS, it is probably due to the drug...But if it worked in refractory patients, it might (be able to overcome that)...Why is Bextra (Pfizer, valdecoxib) not on the market? Because it causes SJS in the neighborhood of 1 in 1,000 – and there are many alternatives."

After the meeting, the panel chair said if Cephalon does another trial it "needs to do it right." And he criticized the company's data in general, saying, "The ambiguity in this (SJS) case just killed them." But there were also criticisms of more than the data on SJS.

The current status is: FDA issued an approvable letter last fall, and the company had six months to respond, which it reported did recently. The FDA approvable letter cited three issues but did not specify that the company had to do a new trial to resolve these issues:

1. Skin rashes.
2. Psychiatric side effects.
3. LFT elevations for which the FDA wanted additional data.

Now, the FDA has 6 months to act again on Cephalon's response to the original approvable letter, and it can issue either:

a. New approvable letter – most likely.
b. Approval – not going to happen. Dr. Temple said flatly, "We won't approve it until we have more data."
c. Reject it – very unlikely.

Thus, the ball is in Cephalon's court, but a source suggested the company may drop trying to get the ADHD indication altogether rather than doing either of these trials.

THE FDA PERSPECTIVE

Dr. Glenn Mannheim, a medical reviewer in the FDA's Division of Psychiatry Products, argued strongly against approval, citing serious safety issues. He stressed that the dose proposed for children (340-425 mg QD) is a much higher dose than is used for adults (200 mg QD). Cephalon is recommending children be titrated up to the full dose, starting at 85 mg and increasing at 85 mg increments.

Modafinil Drug Exposure

Patient population	Dose	Drug exposure	Comparison to adult dose
Adults	200 mg QD	2.67 mg/kg	---
Children <30 kg	340 mg QD	21.25 mg/kg	7.9 times higher
Children ≥30 kg	425 mg QD	14.2 mg/kg	5.3 times higher

The key safety issues for the FDA reviewer were:

1. **Psychosis.** There were five reported cases of psychosis, including two with hallucinations and six suicidal events, (5 suicidal ideations and one unsuccessful attempt). There were no deaths.
2. **Serious skin reactions.** In adults there have been six reports of serious skin reactions, including five biopsy-

confirmed cases of Stevens Johnson Syndrome. In children taking modafinil for ADHD, there have been two cases of SJS as well as other rashes.

a. **Case 1 – progressed after drug discontinuation –** a 7-year-old girl who developed a rash on 425 mg/day on Day 16 that progressed extensively even after modafinil was withdrawn. The SJS finally resolved at Day 30, but a rash returned when she was re-challenged, and she was withdrawn from the study. Her SJS is resolved, but she has continuing erythema multiforme (EM).

b. **Case 2 – hospitalization –** an 11-year-old girl who developed pruritic urticaria on 100 mg/day. The rash worsened even after the drug was stopped and she was hospitalized for SJS. After a week, the rash resolved.

c. **Case 3 –** an 8-year-old boy on 200 mg/day who developed a severe rash at Day 17 but who recovered when the drug was stopped.

d. **Case 4 – hypersensitivity reaction –** a 9-year-old boy on a sulfa drug who developed severe urticaria, liver elevations, face edema, and fever on modafinil, but who recovered when the drug was withdrawn.

Modafinil Adverse Events in Phase III Trials

Side effect	Modafinil	Placebo
Headache	20%	13%
Insomnia	27%	4%
Anorexia	16%	3%
Weight loss	4%	1%
Psychosis	0.5%	---
Suicidal events	0.6%	---
Rashes	4%	2%
Dropouts due to rash	0.24%	0

Dr. Mannheim called modafinil a "public health issue." He estimated that, if modafinil achieves a 10% market share of the 2.5 million children believed to be on ADHD medications, there will be 500-3,250 cases of erythema multiforme or SJS, which is a 0.2%-1.3% incidence. He also estimated there would be 25-488 deaths for each 10% of market share, assuming a 5%-15% mortality rate with SJS. He added, "ADHD is a serious condition usually not considered to be associated with a fatal outcome…The relationship of (modafinil) to rash is speculative, but it has structural similarities to drugs known to cause EM/SJS, which can be fatal. The incidence of EM/SJS in these studies is, at minimum, hundreds of times background…Doses lower than 340 mg have been shown to limit efficacy, hence dose reduction is not a reliable option."

Labeling will not work, he insisted, citing expert testimony at another FDA panel:

"*There is no satisfactory method for determining who is at greatest risk for developing drug-associated SJS...short of avoiding drugs altogether. There has been a single study suggesting that early withdrawal of the agent at the first sign of the illness may improve the outcome…Even if (that) is proven correct, its practical application will be limited because it is very difficult to identify the very earliest lesion in a timely manner because of the rapidly progressive nature of this illness and the non-specific features of its prodrome.*"

The internal debate within the FDA on the safety of modafinil became clear with the second FDA official speaking. The FDA's Dr. Andreason took a much less concerned approach to the safety of modafinil for ADHD. He said, "If SJS were a problem…we should see more of it…When we looked at the post-marketing experience, we didn't look at patient-year incidence, because it would likely show up in the first 2-8 weeks, and using a patient-year (analysis) would lower the background rate."

He appeared to be suggesting that the issue is the risk management program more than approval. He noted that:

➢ **Psychosis.** The rate of psychosis with modafinil ranges from 3.8-15.4 per 100 patient years, a rate that is not statistically significant. Strattera, which has a suicide warning in its label, does have a statistically significant risk (by FDA analysis, not the Lilly analysis).

➢ **Severe rash (EM/SJS).** He said there were 10 dropouts due to rash vs. none with placebo, and he described the two cases of serious rash, but pointed out that neither child was admitted to the ICU or burn unit, which is where SJS cases are usually treated. Furthermore, he pointed out that there have been no cases of SJS reported in the 36,000 patients who have received modafinil off-label for ADHD, though this may have been at a lower dose of 200 mg/day. He said, "In post-marketing for modafinil (for all uses), there have been three confirmed cases of SJS out of 1.5 million patients, which is getting close to background (rates)."

The FDA's invited consultant on SJS, Dr. Michael Bigby of Harvard, spent most of his time explaining the seriousness of SJS and how to diagnose it, but he also appeared to weigh in on the "risk is acceptable" side. He emphasized that erythema multiforme is a distinct disorder, not a variation of SJS. Asked by a panel member how concerned he is with the SJS cases in modafinil patients, he said, "I think the 7-year-old to me was probably SJS and was probably drug-related…I think the drug is going to be, and probably already is, associated with excess cases of SJS."

He made two other interesting comments:

- The SJS prognosis might be worse with higher drug doses since they take longer to clear the body, but higher doses shouldn't affect the incidence of SJS.
- Concomitant use of sulfa drugs (sulfones) probably are not a risk factor for SJS with modafinil. He said, "I think the sulfones may be a red herring…I don't think the sulfone (avoidance) would give us any assurance of safety."

The FDA's Dr. Robert Temple also made an interesting comment that the increase in dose in children compared to adults is on an order of magnitude greater than the FDA is accustomed to seeing, adding, "I can't say a marked difference in blood levels might not be related to the rate (of SJS)."

CEPHALON'S PERSPECTIVE

Cephalon officials and company experts defended the efficacy and safety of modafinil.

➢ Dr. Joseph Biederman, a psychiatrist from Massachusetts General Hospital, speaking for Cephalon, emphasized the seriousness of ADHD, calling it a "lifelong brain disorder of genetic etiology and poor prognosis."

➢ Dr. Srdjan Stankovic, vice president of neuroscience clinical research at Cephalon, reviewed safety issues. On psychiatric issues, Dr. Stankovic described 14 cases in detail. He stressed that modafinil as a pediatric exposure of about 24,700 patient-years, with only 7 cases of psychosis, mania, or suicidality.

With respect to the LFT elevations, Dr. Stankovic said:

- No. 1 had no other lab or physical abnormalities, bilirubin was normal, and the LFT resolved with continued modafinil therapy.
- No. 2 had no other lab or physical abnormalities, bilirubin was normal, and the patient was taken off modafinil.
- No. 3 had normal bilirubin and the abnormal LFT returned to normal after withdrawal of modafinil. It was suggested this may have been a hypersensitivity reaction.

With respect to the skin reactions and SJS, he argued that only one of five patients with serious rashes had probable SJS, but one had possible SJS. He said Cephalon's independent review panel did not believe the 11-year-old

Modafinil Adverse Events in Pediatric Studies

Side effect	Modafinil n=420	Placebo n=213
Serious adverse events in Phase III trials	18 patients	N/A
Additional serious adverse events in ongoing trials	3 patients	N/A
ALT ≥3xULN in all trials	<1% (3 patients)	<1% (1 patient)
ANC >1 - <1.5	6%	4%
ANC ≥1.5	92%	93%
WBC (10E9/L) ≤3	2%	1%
WBC ≥4	87%	90%
CV adverse events	2% (10 patients)	1% (3 patients)
CV adverse events leading to trial withdrawal	0.5%	0.5%
Serious CV adverse events	0	0
Rashes		
	n=664	**n=308**
Non-urticarial rash	4.8% (32 patients)	3.2% (10 patients)
Severe non-urticarial rash	0.6% (4 patients)	0
Psychiatric events		
	n=664	**n=308**
Psychosis/mania	0.5%	0
Suicidal ideation/behavior	0.6%	0
Aggression and violent behavior	1.4%	1.6%
Miscellaneous serious psychiatric events	0	0

Patient Exposure to Different Modafinil Doses

Dose	FDA estimate of patients exposed in Phase III trials	Cephalon estimate of patients exposed in Phase I-III trials
≤255 mg/day	62 patients	167 patients
340 mg/day	102 patients	316 patients
425 mg/day	256 patients	450 patients

Psychotic Events and Suicidality with Modafinil in Pediatric Studies

Patient	Adverse event	Treatment days to onset	Modafinil dose (mg/day)	Duration of event	Action taken
6-year-old boy	Hallucinations	6 days	300	1 day	No treatment, modafinil continued
8-year-old boy	Formication (delusional parasitosis)	18 days	100	2 days	No treatment, modafinil withdrawn
8-year-old boy	Hallucinations	11 days	425	5 days	No treatment, modafinil withdrawn
8-year-old boy	Psychotic disorder, aggravated	19 days	300	7 days	Hospitalized, modafinil withdrawn
7-year-old boy	Ideas of referential control	59 days	340	>10 months	No treatment, modafinil continued
7-year-old boy	Suicidal statement	22 days	200	1 day	No treatment, modafinil continued
10-year-old boy	Suicidal statement	8 days	200	1 day	No treatment, modafinil continued
8-year-old boy	Voiced vague suicidal statement	13 and 21 days	255	1 day	No treatment, modafinil continued
8-year-old girl	Suicide threat	8 days	340	2 days	No treatment, modafinil withdrawn
6-year-old girl	Abnormal behavior	93 days	255	97 days	Hospitalized
15-year-old girl	Situational depression	N/A	425	Ongoing	No treatment, modafinil continued
15-year-old girl	Suicidal ideation	219 days	425	8 days	Hospitalized, modafinil withdrawn
10-year-old girl	Suicidal gesture	75 days	400	1 day	No treatment, modafinil continued
8-year-old boy	Paranoid reaction	18 days	255	5 days	Modafinil discontinued

had SJS, and the three other cases were thought to be: fifth disease, possible herpetic gingivostomatis (though it was acknowledged that this was a possible SJS), and hypersensitivity reaction.

➢ Dr. Victor Raczkowski, Cephalon's vice president of worldwide regulatory affairs, said, "We have seen no cases of SJS in over 30,000 patients."

➢ Dr. Lesley Russell, senior vice president of Cephalon, reviewed the efficacy of modafinil in ADHD trials, showing in graph form how it performed better than placebo in all the studies. She concluded modafinil showed:

- Consistent efficacy results across three pivotal trials.
- Improvement of ADHD symptoms, as evaluated by teachers, parents, and physicians.
- Improvement seen at school, home, and across the day.
- Improvement in core ADHD symptoms/behaviors as well as other psychosocial domains.
- Efficacy in both treatment-naïve patients and in patients with prior stimulant experience.

PUBLIC WITNESSES

There were only a few public witnesses at the modafinil panel. Among their comments were:

➢ *North Carolina psychiatrist:* "Stimulants re-wire the brain …Don't just look at current diversion or abuse (of ADHD drugs), but that these drugs are altering the plasticity of the brains of these children that increases the likelihood of addiction to nicotine or cocaine…People arriving on college campuses who got stimulants (for ADHD) have a (much higher) rate of drug abuse...I (also) believe it is time for the FDA and physicians to look at growth suppression (with ADHD drugs) – on long bones, the skull, and the brain…The third elephant in the room is the effects on cortical blood flow, specifically the frontal and temporal cortex…There is a real causal effect that deserves a black box at least so parents are aware it (a stimulant) can shrink the cortex."

➢ *A Michigan anti-psychiatry activist:* "What's next FDA? Are you going to accept jetlag as a disease?"

➢ *North Carolina pediatrician:* "Claims for effectiveness are exaggerated…And it (modafinil) has a potential for abuse even greater than stimulants…Approval is premature…The FDA would be better served by exercising caution than by opening the door for even more criticisms than has emerged over stimulant drugs."

PANEL DISCUSSION

Efficacy was not an issue to either the panel or the FDA. The panel chair said, "The FDA says they are satisfied (with efficacy), and I certainly feel satisfied with what I've seen." Thus, the debate focused on safety issues.

Among the issues of concern to the panel were:

➢ ***Whether there is value to modafinil when there are already several approved ADHD drugs.*** Company officials and experts responded that:

Patients who failed another agent may respond to modafinil. However, the FDA's Dr. Temple warned the committee that there is no evidence of this, "I am sympathetic that drugs of different pharmacology may have different utility...but have they documented that this (modafinil) works in people resistant to stimulants? No, they have not shown that. There is a simple study to show that, a perfectly simple study. That study could be done, but it has not been done. To say that people respond to a second drug when the first doesn't work tells you nothing. They have not shown that. It is plausible but not shown."

Less likelihood of abuse or diversion. A Cephalon official said, "The attraction (to addicts) of stimulants is that a tablet can be crushed and snorted…This drug (modafinil) is not a drug that the addict community on the street would buy for a high." Another Cephalon official said, "In human studies, it was demonstrated that in males there is no stimulant-like effect of modafinil…There is some reinforcing quality, but it is very, very weak…(However) monkeys trained to cocaine would administer large doses of this like they would with other drugs." Another Cephalon official cited these reasons that modafinil may have a low potential for abuse:

- Low water solubility, so incompatible with IV injection.
- Unstable at high temperatures, which is incompatible with smoking.
- Structurally unrelated to known addictive agents of abuse.
- Lack of activating of reward centers at pharmacologically active dosages.
- Does not cause release of dopamine in vitro or in vivo.
- Results from non-clinical abuse liability studies consistent with low abuse of potential.
- Post-marketing surveillance continues to support the conclusions that the abuse liability of modafinil, if it exists, is low.

Clinicians and patients need other options.

➢ ***Whether approval would give modafinil a marketing advantage over other ADHD drugs.*** Modafinil is classified as a Schedule 4 drug by the Drug Enforcement Administration, but the amphetamine and methylphenidate agents are Schedule 2, which is more tightly controlled. A panel member wondered, "If this were approved, how will it be marketed and what are the messages? We've seen situations where something was marketed as 'free of something else,' suggesting there are no risks. To say that because modafinil is a non-stimulant that it has no risk would be a concern to me." Dr. Temple responded, "We are careful about claims (made by companies) when there is no direct comparison…We are very

careful about comparison in the absence of comparative studies…However, if one is scheduled in a different place, they would be able to claim that."

➢ ***Whether modafinil should be considered a stimulant even if it is not technically a stimulant.*** A Cephalon official said, "It is a CNS activating agent – a non-traditional agent."

➢ ***The level of risk of SJS.*** Dr. Bigby, the dermatologist consultant on the panel, said, "There is one case of SJS and a signal of exanthema…The majority of SJS cases occur in 1-4 weeks or probably 1-3 weeks." The panel and FDA were concerned that the incidence might be under-reported.

The principal investigator who reported the 7-year-old boy with probable SJS was asked to provide more detail on the case, and his credibility appeared to be an issue. He said he initially saw the boy and prescribed modafinil, but the boy was seen by another investigator or a pediatrician for the next month. He didn't see the boy again for four weeks, yet he was the one who wrote most of the descriptions and narratives on the case. He said, "None of the investigators saw the patient when the rash was present…I did most of the write-ups… There are a lot of errors in the (patient) history."

➢ ***Cardiac safety.*** The consensus appeared to be that modafinil should be considered to have the same issues as other approved ADHD drugs and the label should warn against use in children with known structural abnormalities of the heart.

The dermatologist on the panel said, "That sounds like SJS…In population-based studies, the estimate is one case of SJS in 500,000-1,000,000 patients, and a case-controlled study in Europe that tried to identify all the cases over a period of time…estimated it was 1 in 400,000." Another panel member said, "It is the degree of uncertainty that is what bothers me… That makes me unwilling to say it is fine or perfectly acceptable to proceed with people just having to report rashes."

Among the other comments on this issue were:

- An FDA staffer asked the investigator which report was true – his written one or the verbal one he gave the committee.
- *FDA's Dr. Laughren:* "Under-reporting is probably high…but something like SJS is a serious and alarming event and probably much more likely to be reported, but the truth is that we don't know the extent of under-reporting."
- *FDA's Dr. Temple called SJS a "scary and life-threatening condition":* "This goes to the heart of it…If you believe there is one case, then you have the lower boundary, but how reassured are we that all the pediatric use hasn't produced any (cases)…And you can't take reassurance because people report poorly…I take a little reassurance, but it is hard to know. That's what's at the nub of this – the things you can do to try to manage that risk, taking some risk – or ask for more data."
- *Dermatologist:* "We have reason to worry but not enough data to say it is not safe."
- *Cephalon official:* "I think there could be strength to the argument that one case of SJS is a fluke. This is not Lamictal (GlaxoSmithKline, lamotrigine, a treatment for bipolar disorder) where SJS was seen right from the beginning. Lamictal was a drug with a very different risk, and I think that has been managed over the years…I can't really confidently say there will be cases of SJS in this (modafinil)...I don't see that with the exposure we have."
- "I'm left with a lot of questions and a lot of lack of confidence…and I feel like erring on the side of conservatism – either longer testing or saying no (to approval)…I feel the public needs to be protected."

➢ ***Whether the insomnia side effect is related to dose or time on treatment.*** A Cephalon official said the insomnia appears to start with treatment initiation (during the first two weeks, and then appears to taper off, "There appear to be people who learn to get used to it or habituate to it. We looked at dosages, and there doesn't appear to be difference by dose."

THE FDA'S QUESTIONS TO THE PANEL

QUESTION 1. Has modafinil been shown to be effective for the treatment of ADHD in children and adolescents?
Unanimously Yes

Panel member comments included:

- *Chair:* "I am satisfied that there is sufficient efficacy data."
- "It looks clear to me that there are not a lot of questions about efficacy…On the face of it, there is a reasonably strong case for efficacy here…It would appear the abuse potential is less than some of the stimulants, but we often don't find out about abuse potential until a medication becomes widely available in a particular population."
- "This is a medication that looks somewhat less effective than the other options available, and it has the common and mild side effects very similar to the other agents, so it would be a fourth- or fifth-line medication I might turn to…We have heard that physicians might want to use this because it is not a controlled substance…I don't like that argument…I don't see that as persuasive…The argument of less abusability might be attractive to me if I were looking at a family where I thought abuse might be possible, but I have other agents that I could turn to."

QUESTION 2. Has modafinil been shown to be acceptably safe in the treatment of ADHD in children – cardiac, dermatologically, growth, and psychiatrically?
No 12, Yes 1

Panel member comments included:

- *Dermatologist (the one yes vote):* "This is a case where we are asked to make a decision on a single case that is probable but not definite…I have concerns that when the drug is more widely used, you will see cases of Stevens Johnson Syndrome, but you see that with lots of other drugs that are already marketed."
- *Chair:* "My comfort level is not sufficient that this is acceptably safe…I don't know what to make of the one case (of SJS), and frankly I don't think we will ever be sure…but it raises sufficient doubts about serious adverse events...I'm not willing to find the risk acceptable without additional data that would arrest some of my concerns on the dermatological reactions."
- "I really don't think it is that big a deal to cap this (SJS risk) at 1 in 1,000, so I would recommend a 3,000-patient trial, with patients treated for a month."
- "I think additional information will help with compliance. If this were approved now, regardless of how the clinician might feel, the compliance of parents would perhaps not be as good as if there were a clearer view of the risks where they could make an informed decision…I think we need more data, and it is worth the wait."
- "I think we need a study specifically designed to get a good estimate of the rate (of SJS)."
- "I don't believe the case for safety has been adequately made…and I don't think we are convinced it is more effective – and perhaps is not as effective – as available treatments...We have reasons to suspect the incidence of an uncommon side effect is higher with this."
- *Patient representative:* "The uncertainty with all this today has been almost painful, so I think we do need more information before we can put it out for the public."
- *Non-voting industry representative:* "I'm not convinced this (one case) was SJS…I would have voted yes (modafinil is safe)."
- *Chair:* "I don't believe modafinil has been shown to be acceptably safe…If it (the SJS rate) is 2 per 1,000, I think we would all regret going forward…I wouldn't want to do that experiment in the post-marketing arena….but if we recommend studies, I hope we don't set the bar too high…I think this is a drug we all agree is efficacious and may have advantages over certain compounds…I would like to see an opportunity for the company to come back with those additional data and to show that this case was a fluke, and that could be what it was."
- *FDA's Dr. Laughren:* If we cap the risk at 1 in 1,000 patients, and we are comfortable with that cap, the drug would still have fairly strong labeling…That (a rate of 1 in 1,000) won't make the problem go away."
- *FDA's Dr. Temple:* "If there were no other treatment for ADHD, we wouldn't be having this discussion."

After the advisory committee meeting ended, Cephalon officials said they were "extremely disappointed" in the results of the advisory committee meeting. An official said the company will be meeting with the FDA "trying to get a handle on what the future plan for Sparlon is and what the future path forward is for this drug and ADHD."

Another Cephalon official said the panel's attention to the SJS case surprised them "because there hadn't been that much of a concern with the mother of the child…It wasn't a concern enough for the pediatricians to hospitalize the child, and so we were taken by surprise when we saw the degree of concern (of) this relatively benign case…The case occurred 18-24 months ago…It seems to me the agency is more cautious than it has always been...We're just caught up in a general heightened sense of concern about safety issues, disclosure, potential safety issues, rather than actual safety issues. And we're part of that concern now, obviously, which is made more complicated by dealing with children and adolescents, where the emotions are even higher than for adults."

♦