Transcript for FDA Media Briefing
on Safety Labeling Changes for Antipsychotic Drugs
June 16, 2008

Coordinator: Welcome and thank you for standing by. At this time, all participants are in a listen-only mode. If you would like to ask a question during the question and answer session, please press star 1 on your touchtone phone. Today's conference is being recorded. If you have any objections, you may disconnect at this time.

Now I will turn the meeting over to Miss Sandy Walsh.

Sandy Walsh: Good afternoon and thank you for joining us. This is Sandy Walsh with the FDA's Office of Public Affairs. By now you should've gotten our press release on anti-psychotic drugs. I'm going to let Dr. Tom Laughren -- L-A-U-G-H-R-E-N -- explain to you what the FDA's action today is, and then we'll open up the line for questions and answers. Dr. Laughren?

Tom Laughren: Okay. I can begin with a brief summary of the action that was taken today and what we hope to accomplish with it. We issued letters to manufacturers of all the anti-psychotic drugs both conventional and atypical, requiring them to update their labeling with new language, for a boxed warning about an increased risk of death in elderly patients with dementia.

For the conventional anti-psychotic drugs, this will involve entirely new language. For the atypical drug, this will involve a slight revision of a boxed warning that was already implemented in 2005. Now the boxed warning will say that elderly patients with dementia-related psychosis, who are treated with anti-psychotic drugs have an increased risk of death.

The statement will then go on to describe the meta-analysis that FDA conducted for atypical anti-psychotic drugs back in 2005. And that was the basis for the original action back then. It will then go on to say that recent observational studies with anti-psychotic drugs used in this population, suggests that this same risk appears to be present for the conventional drugs as well.

Now anti-psychotic drugs -- both atypicals and conventionals -- are used primarily to treat major mental illness, in particular schizophrenia and bi-polar disorder. However, they have been used in other settings including use in treating various behavioral symptoms associated with dementia.

Now the primary symptoms of dementia involve intellectual decline, for example memory loss and impaired judgment and language function. But patients with dementia often have behavioral symptoms as well. For example, they can have psychotic symptoms such as delusions and hallucinations. They can be agitated, aggressive and at times violent. And anti-psychotic drugs are sometimes used in treating these behavioral symptoms.

Now the purpose of this warning is to alert clinicians that there is a risk of excess mortality in using these drugs in this population. We first added this language for the atypical anti-psychotics in 2005, based on the meta-analysis that I mentioned. We did not include the conventional anti-psychotic drug in that original action because we did not have data to support such an action.

The data we now have from observational studies are not ideal. There are potential biases that complicate the interpretation of these data. And so we've struggled with this decision. But in the end we've decided that the data are strong enough overall to be of sufficient basis for extending this warning to all drugs in this class.

It's important to emphasize that this is not a contra-indication. Clinicians still have the option of using these drugs to treat this aspect of dementia at their discretion. However, they are not approved for this indication. And we do want clinicians to be aware of the risks in using drugs in this population if they choose to use them.

So I'll stop there and I'm happy to take any questions.

Sandy Walsh: Operator, can we open the lines for questions please?

Coordinator: Thank you. We will now begin the question and answer session. If you would like to ask a question, please press star 1. Please un-mute your phone and record your name clearly when prompted. Your name is required to introduce your question. To withdraw your request, you may press star 2. Once again to ask a question, please press star 1. One moment please for the first question.

(Delian Trobriner), you may ask your question.

(Delian Trobriner): Thank you. Actually it's two questions. One is you mentioned in the press release that there are no alternative drug treatments, but there are other things one can do. If you could talk about that -- and two is the deaths seem to be caused by heart failure, cardiovascular disease, pneumonia. What would the mechanism there be?

Tom Laughren: Okay. It's true that there are no other drugs that are approved for treating behavioral symptoms associated with dementia, that there are other drugs that clinicians use. In terms of other treatments, there are a variety of behavioral strategies that have been developed to try and help patients with these symptoms.

These are mostly patients in long term care facilities, nursing homes and so forth. And various groups have worked out strategies of trying to create familiar environments. These patients tend not to like change. They like to have routine. And some of these strategies have had some success in dealing with these problems, but not entirely and clinicians often feel that they have to resort to medication.

In terms of mechanism, we really don't understand the mechanism. In the meta-analysis that we did with the atypical drugs, the two major types of death were cardiovascular and infection, so a patient's dying of pneumonia. In one of the observational studies that was the basis for our action today, there were some patients who were dying of cancer death.

We really don't understand exactly what the mechanism is. There are a variety of possible mechanisms. But I think it's best to say at this point that we just really don't understand the mechanism.

(Delian Trobriner): Thank you.

Sandy Walsh: Next question, please.

Coordinator: (Steve Levin), you may ask your question.

(Steve Levin): The press release notes that the label changes being requested under FDA. And I'm wondering is this the first time that FDA has exercised that authority into the law?

Tom Laughren: I don't have an answer to that question. I mean this is the first time in my division where we have utilized this authority. But I don't -- and overall I

can't say. I mean this is a new authority that arises from the FDA Amendments Act of 2007. It's the first time that we have had actual authority to require companies to make certain safety related changes. We think it's an important authority and we welcome it. But we'll see how it works out.

Sandy Walsh: This is Sandy Walsh. I am checking on that to see if it is actually the first time, and I'll get back to you on that.

(Steve Levin): Great. Thank you.

Sandy Walsh: Next question, please.

Coordinator: (Brian Hardeman), you may ask your question.

(Brian Hardeman): It was answered already. Thank you.

Sandy Walsh: Next question, please. And if (Curtis) could announce your name and affiliation, please.

Coordinator: (Matt Carone), you may ask your question.

(Matt Carone): Hi. It's (Matt) with (Assist-da-Prep). Could you just give us a little background on how old the typical anti-psychotics are? Are they mainly generics now? Because just my sense is that for the most part, these treatments have sort of been replaced by the newer drugs. But I want to make sure that's accurate.

Tom Laughren: Well the conventional anti-psychotic drugs like Haldol and Mellaril and Thorazine and so forth, that are now almost all generic have been around for

many decades. These drugs were first introduced in the late ‘50s and the ‘60s and ‘70s. So they’re very old.

The atypical anti-psychotic drug are more recent of course. They haven’t entirely replaced the conventional drug, either for their primary uses or for these off-label uses in treating behavioral symptoms in dementia. I couldn’t give you an exact breakdown of what proportion of the treatment is for each.

But it meant it’s sure that the atypical drugs have been, you know, are very readily picked up and are widely used. But there is still some use of the conventional drug.

(Matt Carone): And do they have an advantage -- the newer drugs? Is there a reason that -- are they more effective?

Tom Laughren: No. There’s no direct evidence that they’re more effective. But the major apparent advantage is it’s less side effects.

(Matt Carone): I see.

Tom Laughren: The newer drugs tend to have less various motor side effects, what are known as extrapyramidal symptoms -- tremors and rigidity and Parkinsonian symptoms and so forth. And that’s primarily the reason why they’re more widely used.

(Matt Carone): Thank you.

Sandy Walsh: Next question, please.

Coordinator: Bridget Kuehn, you may ask your question.

Bridget Kuehn: Hi. My name is Bridget Kuehn. I'm with the JAMA Medical News. I have a couple of questions. Just a follow-up on the last question -- if these drugs have been around for so long and the atypicals have been around for a while now too, why are these side effects or this -- in this particular group kind of emerging now?

Tom Laughren: You're talking about the side effect of excess mortality? Well we first recognized this as a problem three years ago...

Bridget Kuehn: Okay.

Tom Laughren: ...when last we did a meta-analysis of the placebo control trials for the atypical drug. And that was the basis as I mentioned for adding this boxed warning to the atypical drugs three years ago. We don't have the same kind of data for the typical drugs.

So I mean these drugs again were developed many, many years ago often not in the context of placebo control trials. And so we don't have comparable data. In trying to address that, several groups have looked at used observational methods.

These are basically epidemiologic strategies, non-randomized studies. And it was based on these two recent observational studies that we finally reached the conclusion that it was time to extend this warning to the conventional drugs. It's very difficult to determine a causality for a death in this population because the background risk of death is so high.

I mean you really only can do this in the context of a controlled setting, either again a placebo controlled randomized study, or an observational study where

you have a control group. You wouldn't be able to interpret an individual death in a patient. These patients in the studies we looked at had an average age of around late 80s. I mean...

Bridget Kuehn: Okay.

Tom Laughren: ...you're talking about very elderly people.

Bridget Kuehn: And also how -- just to give, you know, the physicians are going to read about this in context. How do you think that these new -- the revised warning for the atypicals and the new warning for the typicals -- should change the sort of the way physicians do their risk benefit analysis for these drugs in this population?

Tom Laughren: Well as I mentioned the change in the warning for the atypicals is very minor. And basically it just mentions that we now consider this risk to extend to the conventional drug. For the conventionals, it's an entirely new warning. They previously didn't have a box.

In terms of how this would impact on their practice, as I said this is not a contra-indication. We're not telling clinicians that they absolutely cannot use these drugs in this setting. What we want to do is make them aware of this risk.

And this is something that we would hope that they would discuss with -- in this case it's not so much discussing it with these patients because these patients have dementia, but with the families and the caregivers so they can understand that there are risks in using these drugs.

But this is a very difficult situation to manage these patients. They're very sick. As I mentioned, sometimes these patients can become very aggressive and violent and they can injure other patients, themselves, other staff and so forth. So it's a very difficult situation to manage clinically.

Bridget Kuehn: Thank you.

Coordinator: Next question -- Shenkar Vedantam, you may ask your question.

Shenkar Vedantam: Shenkar Vedantam at the Washington Post. Doctor Laughren, could you give us a quick sense of what the difference in mortality was, between drug and placebo in your meta-analysis for the atypicals? And can you also just give us a quick overview of where things stand with black box warnings on anti-psychotics in general? Are they applied only to the elderly? Is it for other groups? Can you just bring us up to speed with where things stand?

Tom Laughren: Okay. In terms of the size of the effect, if you look at the black box for the atypicals that's out there now, basically it describes the results of our meta-analysis. And what that found is that -- and this is -- the timeframe here is roughly -- these are roughly ten week studies.

So the risk of dying -- and this is very high keeping in mind that this is a very elderly and very sick population. Roughly 4-1/2% of those patients died over that timeframe of those assigned to drugs, about 2.6% on placebo. So it's, you know, it's a very substantial risk of mortality both in those who get drugs and those who don't. Of course it's a concern to us that it's higher in those who get drugs.

Shenkar Vedantam: So 4.5% in the drug arm and 2.6% on the placebo arm?

Tom Laughren: Right.

Shenkar Vedantam: Okay.

Tom Laughren: This is a risk difference of roughly 2%.

Shenkar Vedantam: Okay.

Tom Laughren: And in the terms of the observational studies, I don't have those data in front of me. As I mentioned there are problems interpreting observational studies. These are not randomized. There are potential -- there's potential compounding.

If for example the patients who were prescribed the conventionals were sicker to begin with and had a higher risk of death that, you know, could give a biased result. So we don't think those studies are particularly useful in addressing the relative risk of atypicals versus conventionals. But we felt overall it was strong enough to support extending the warning to the conventionals.

And I'm sorry -- the second question again?

Shenkar Vedantam: If you could just give us sort of a quick overview on where things stand with black boxes in anti-psychotic drugs in general. Are they limited now exclusively to elderly populations, to everyone? Is it only the dementia issue? Is it other issues?

Tom Laughren: Well this finding is specifically in patients with dementia.

Shenkar Vedantam: Okay.

Tom Laughren: There is concern about mortality for anti-psychotic drugs overall. There are some epidemiologic studies that have looked at this. And we're actively looking at those now. We don't have the same kind of controlled trial data with a sufficient number of deaths to do the kind of meta-analysis that we did with the -- in this dementia population.

Shenkar Vedantam: Okay.

Tom Laughren: But we do have a concern overall about this risk. And it is actively being looked at.

Shenkar Vedantam: But it's accurate to say that as of now, the black box warning on anti-psychotic drugs are limited exclusively to elderly patients with dementia?

Tom Laughren: Yes.

Shenkar Vedantam: Okay. Thank you.

Sandy Walsh: Is there another question?

Coordinator: I show no further questions at this moment.

Sandy Walsh: Is there anyone else that would like to ask a question of Doctor Laughren?

Coordinator: Once again if you would like to ask a question, please press star 1.

Sandy Walsh: Okay then. Okay. We can take the next question, please.

Coordinator: Shenkar Vedantam.

Shenkar Vedantam: Yes. This is Shenkar at the Washington Post once again. Doctor Laughren, could you just give us a quick sense about where things stand on the suicidality issue as well? Has there been any work done on anti-psychotics looking at that question? Or is that been limited exclusively to the anti-depressants? Has that been an issue at all (unintelligible)?

Tom Laughren: It's a fair question. And, you know, we've thought about doing a similar meta-analysis with the anti-psychotics. We haven't done that as yet.

Shenkar Vedantam: Okay.

Tom Laughren: When we undertake these meta-analyses as you can imagine, it's a very major undertaking. So it's something we've thought about. But no, we haven't actually begun that yet.

Shenkar Vedantam: Okay. All right. And when do you expect that if at all you might have sort of the finding on the other aspects on anti-psychotics -- not the suicidality, but just sort of the weight gain issue and the other things? When might that analysis be complete?

Tom Laughren: Well this really began with our looking in more detail at Olanzapine. And that label has already been substantially changed as of last fall, to more fully reflect the metabolic risks of that drug.

We have gone ahead and we've asked all the other anti-psychotic manufacturers to give us similar data on metabolic risks with the other drugs. And we're just now beginning to get that data. I would think it's going to take us, you know, the better part of the next six months to a year to work through that and implement changes for the other drugs.

Shenkar Vedantam: Okay. And you don't have any users numbers whatsoever on the use of these drugs among the elderly, right? I mean you don't how many elderly get anti-psychotics, how many get conventionals?

Tom Laughren: The problem that we have -- the use data that we have best access to at FDA is outpatient data.

Shenkar Vedantam: Right.

Tom Laughren: And these drugs are used primarily in long term care facilities. We're trying to figure out ways of getting better use data on these drugs. One of the interesting questions that we tried to look at is whether or not subsequent to the boxed warning in 2005 for the atypicals, there was a shifting of use from the atypicals to the conventionals.

Again, unfortunately we don't have the best data to look at that. But from what we can see it didn't appear - there didn't appear to be a strong shift. But again, we don't have the optimal data for looking at that question.

Shenkar Vedantam: Okay.

Sandy Walsh: Okay. Next question, please.

Coordinator: (Mary Brophy-Marcus), you may ask your question.

(Mary Brophy-Marcus): Hi. I know you said that the study reflected 80 year olds. But if the black box warning is indicating the elderly, are we to assume our 65 year old father applies to that warning as well? Or...

Tom Laughren: I think it's fair to assume that this refers to yes, 65 and above.

(Mary Brophy-Marcus): Okay. Thank you. That's all.

Sandy Marcus: Okay. Next question, please.

Coordinator: Jeff Evans, you may ask your question.

Jeff Evans: Hi. I'm Jeff Evans with the Clinical Psychiatry News. I was just wondering if you could describe some of the drugs that are out there that are not necessarily approved for, you know, demented individuals but are actually used, you know, that could be used instead of these conventional anti-psychotic?

Tom Laughren: Well again I want to make clear that I'm not advocating or promoting these. But various benzodiazepines have been used for treating behavioral symptoms in (unintelligible). And some of the anti-epileptic drugs have been used. But there aren't, as I mentioned, none of these are approved for treating these symptoms. And the data are very mixed about the success of any of these in treating these patients.

Jeff Evans: Okay. Thanks.

Sandy Walsh: Okay. Next question, please.

Coordinator: John Gever, you may ask your question.

John Gever: Hi. This is John Gever with MedPage Today. I was just wondering about the exact language of the warnings, of both for the conventionals and the revision for the atypicals. Is that available on the Web site somewhere?

Tom Laughren: Sandy, do you know if...

John Gever: Like copies of the letters that were sent out?

Tom Laughren: The letters went out this morning. Do you know if...

Sandy Walsh: I can check on that. Usually the new draft labeling goes out pretty quickly on drugs at FDA. But the letter -- actual copies of the letters are not releasable until they're redacted. But I can look into that.

Tom Laughren: The boxed warning is standard language for now for the conventionals and the atypicals. So it's just a -- it's one standard language. I don't see any problem with releasing that.

Sandy Walsh: Yes. We can get that.

John Gever: Okay. Thank you.

Sandy Walsh: Okay.

Coordinator: Our final question comes from Nancy Faigen. Ma'am, you may ask your question.

Nancy Faigen: Yes. It's Nancy Faigen with Scrip Pharmaceutical News. I was wondering how large are those observational studies? And did I hear you say you weren't sure where they were published? Or do we have (unintelligible)?

Tom Laughren: Oh no. They're -- the exact references are mentioned in the sheet.

Sandy Walsh: Yes. In the healthcare providers sheet that was released today, the press release has a link in it.

Nancy Faigen: Okay. Thanks.

Sandy Walsh: That key to have some more technical information and the citations are in it.

Nancy Faigen: Okay. Thanks.

Sandy Walsh: Was that your only question?

Nancy Faigen: That's all, yes.

Sandy Walsh: Okay. I believe that's all of our questions for today. This is Sandy Walsh again with the FDA's Office of Public Affairs. Thank you, Doctor Laughren. Do you have any closing remarks?

Tom Laughren: No. I think we've covered all the important issues.

Sandy Walsh: Okay. And I know there was a few outstanding questions. So I'll look these things up for people. And if anyone has any follow-up questions, you can contact me in the FDA's Office of Public Affairs at 301-827-3418, or my email is sandy -- S-A-N-D-Y -- dot walsh -- W-A-L-S-H -- @fda.hhs.gov. And this concludes our briefing for this afternoon. Thank you all for joining us. And thank you Doctor Laughren.

Tom Laughren: Okay. Thank you. Bye-bye.

Coordinator: That concludes today's conference. You may go ahead and disconnect.

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