

**FDA Media Briefing on New Warnings about the Use of Codeine and Tramadol in Certain Children and Nursing Mothers**  
**Moderator: Sarah Peddicord**  
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**1:15 pm EDT**

Coordinator: Welcome and thank you for standing by. At this time, all participants are in a listen-only mode until the question and answer session of today's conference. At that time, you may press star 1 on your phone to ask a question. I would like to inform all parties that today's conference is being recorded. If you have any objections, you may disconnect at this time. I would now like to turn the conference over to Ms. Sarah Peddicord. Thank you. You may begin.

Sarah Peddicord: Good afternoon and thank you for participating in today's call. My name is Sarah Peddicord and I'm from the FDA's Office of Media Affairs. This is a media briefing regarding the FDA's announcement requiring a series of changes to codeine and tramadol prescription drug labeling, in an effort to better protect children and nursing infants from the serious life threatening risks associated with these products. By now a statement has posted to our website as well as a drug safety communication and an update for consumers.

Today I'm joined by Dr. Douglas Throckmorton, deputy center director of regulatory programs in the FDA Center for Drug Evaluation and Research, as well as several subject matter experts from the Center for Drug Evaluation and Research. After Dr. Throckmorton's remarks, we will move to the question and answer portion of the call. Reporters will be in a listen only mode until we open the call up for questions.

When asking a question, please remember to state your name and affiliation and please limit yourself to one question and one follow-up so that we can get to as many questions as possible. I'll also note that since we have several experts with us today, we might be helping to direct those questions to the

most appropriate expert in the room. With that, I'll now turn it over to Dr. Throckmorton.

Dr. Douglas Throckmorton: Thank you Sarah. And good afternoon to those of you on the phone. I appreciate you making time. In the past, I've had the opportunity to speak with many of you about the actions the FDA is taking to combat the addiction, overdose and death brought about by the opioid epidemic. As you know, this is a topic of extreme importance and concern to our agency. Today's announcement, although related to opioid medications, is not related to the abuse or misuse of those powerful drugs.

Today we are taking actions to ensure health care providers and parents are aware of serious risks of two specific types of opioids - codeine and tramadol, due to the unique way these drugs are broken down in the body in some children. Let me give you just a little bit of background. The FDA has been closely examining the safety of codeine and the treatment of pain and cough in children, for the past several years.

Codeine is an opioid that is found in both prescription pain and cough medicines as well as some over the counter cough medicines. The FDA has become increasingly concerned that some children metabolize or break down codeine much faster than is usual – these children are called ultra rapid metabolizers – causing dangerously high levels of opioids in their bodies to build up, that can cause life threatening respiratory depression and even death.

This respiratory depression can also occur in nursing babies when mothers who are ultra rapid metabolizers take the medicine and pass through high levels of the opioid to their children through the breast milk. Another type of opioid, tramadol, is metabolized in a similar way. While tramadol is only

approved for the treatment of pain in adults, we've become aware that tramadol is sometimes prescribed for treating pain in children.

Because we can't easily determine which children or nursing mothers, specifically, are at greater risk of ultra rapid metabolism of codeine and tramadol, today we are requiring manufacturers of prescription codeine and tramadol products, to make important labeling changes to protect those children who are at the greatest risk. These groups include children under 12, adolescents who are obese or have other conditions that may increase their risk of breathing problems, children under 18 who have undergone tonsillectomy and/or adenoidectomy and nursing infants.

Let me give you some specifics. First, a new contraindication will be added to the labeling of codeine and tramadol, alerting health care professionals and parents that these products should not be used in children younger than 12 years of age. Codeine should not be used to treat pain or cough and tramadol should not be used to treat pain.

Second, a contraindication will be added to the tramadol label, warning against its use in children under 18 to treat pain after surgery, to remove tonsils or adenoids. The labels of codeine containing products already carry this contraindication.

Third, a new warning will be added to labels of both codeine and tramadol products, to recommend against their use in adolescents between 12 and 18 years, who are obese or have conditions such as obstructive sleep apnea or lung disease, which may increase this risk of serious breathing problems.

And finally, the warning on codeine and tramadol will be strengthened to inform mothers that breastfeeding is not recommended while they use codeine

or tramadol, due to the risk of serious adverse reactions in breastfed infants such as excessive sleepiness, difficulty breastfeeding or serious breathing problems, which could result in death.

It's important to know, this isn't the first time we've taken action or issued warnings related to the metabolism of codeine. We've already required the prescription codeine labeling contain a boxed warning, regarding the risk of death related to this ultra rapid metabolism of codeine to morphine. And codeine is already contraindicated for post-operative pain management in children up to 18, who have undergone tonsillectomy and/or adenoidectomy.

Today's actions build on our better understanding of this very serious safety issue, based on the very latest evidence. Given the importance of reaching health care professionals and the public with this information, we are also issuing a drug safety communication, to inform both professionals and consumers, about these labeling changes. We also intend to hold a public advisory committee later this year, to discuss the broader role of prescription opioid cough and cold medicines in children, including those containing codeine.

Because many cough and cold products are available over the counter, the FDA also encourages parents to review the ingredients of those medicines and consult their health care provider before giving their children any medicines containing codeine. We continue to assess the risks associated with over the counter codeine containing medicines and will determine whether additional actions need to be taken.

Before I open the call to questions, I want to reinforce that we understand that there are limited options when it comes to treating pain and cough in children.

However, after careful review, our decision to require these labeling updates was taken because we believe it is a way we can protect children who are vulnerable to the associated serious risks of this ultra rapid metabolism of codeine and tramadol. In all situations, we recommend that parents and healthcare professionals consider the best options for treating pain or cough in children, with the risks of codeine and tramadol in mind. Thank you for helping us get the word out about this important safety action. And I'd be happy to answer any questions I can.

Sarah Peddicord: Thank you Dr. Throckmorton. (Sheila), at this time, we'll begin the question and answer portion of the briefing. We'll go ahead and take the first question 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, unmute your phone and record your name clearly. If you need to withdraw your question, press star 2. Again, to ask a question, please press star 1. Our first question is from Leigh Ann Winick with CBS News. Your line is open.

Leigh Ann Winick: Hi. Thank you. Could you shed some light on the over the counter versions? Would you be able to give us some brands or some types where we can look for this?

Dr. Douglas Throckmorton: Let me see if others here can give me some specific names of some over the counter products. If not, we can certainly get that information back to you. There are a variety of products that we're aware of. The major point is again, we want prescribers and patients – family members – to talk to their health care providers before using those medicines.

Leigh Ann Winick: And is there risk, in particular, of adolescents abusing these as some products have gone, you know, other types of products have gone behind the counter? Is that something you're seeing, or is that not a problem?

Dr. Douglas Throckmorton: So the focus of this action today is not on the abuse of opioids at all. It's related to a safety concern. Many of the opioids have a risk of abuse and addiction. We'd have to get back with you about specific risks in the adolescent population for codeine and tramadol. Those products carry those - they have those risks - but I don't know the details specifically, now.

Leigh Ann Winick: Okay. It'd be helpful to our viewers if you could get us those names so we can get a sense of the scope of the OTC products.

Sarah Peddicord: Okay, great. Thank you. We'll follow up with you after the call. Operator, we'll take the next question please.

Coordinator: Our next question is from Linda Johnson with Associated Press. Your line is open.

Linda Johnson: Hello everybody. I'm wondering if you could talk a little bit about what prompted this new warning. I believed you said really quickly, something about new safety information. Do you have new data on children who have died, infants who have been harmed after their mothers breastfed and used these products? You know, what exactly is the reason for this extra concern?

Dr. Douglas Throckmorton: So I'm going to start by just saying again, this is something we've been watching for several years. So we've been working on this issue and as data come in, we've been reviewing it. At this time we've received additional information and we believed this was the right course to take at this time. The

drug safety communication lays out the specific information - the numbers of deaths and other serious injuries that we've had reported to us.

And I'd suggest maybe looking there and we'd be happy to answer other questions if you have them after that.

Linda Johnson: All right. Since you said that there are limited options for treating adolescents with pain and I believe you said cough, are there other ones that you could recommend to parents that are considered safer?

Dr. Douglas Throckmorton: Well I don't want to get into recommending specific products right now. I think it's - I ended the way I did the last question. Talk with your health care professionals, really. Talk to the doctor. Talk about the right best medicines to use for the patient in the specific circumstances, would be my recommendation.

Sarah Peddicord: Great. Thank you Linda. And Operator, we'll take the next question please.

Coordinator: Thank you. Our next question is from Catherine Saint-Louis with the New York Times. Your line is open.

Catherine Saint-Louis: Hi. Thanks for taking my question. So my question is do we have any sense of what percentage of children are these kind of rapid metabolizers? And similarly, do we have any sense of how many adult women are rapid metabolizers? Like is it super rare, or not?

Dr. Douglas Throckmorton: Catherine, I'm going to - very good question. I'm going to ask Dr. Racoosin to help answer that - those.

Dr. Judy Racoosin: Hi. It's Judy Racoosin from the Division of Anesthesia, Analgesia and Addiction Products. So if you look at the external Q&A that was posted along with the other materials, there's actually a table for selected components of the population. But the ultra rapid metabolism is related to the cytochrome P450 isoenzyme 2D6 (CYP2D6) enzyme in the liver that is responsible for metabolizing codeine and tramadol, to their more potent, active metabolites, so the active components that account for the activity at the opioid receptor.

And that is - enzyme CYP2D6 is what's called polymorphic. And I apologize for getting into the technical language here, but it's hard to avoid. That polymorphic enzyme varies by ethnic and racial group. And so it's referring to table 1 in the external Q&A. I can read out the percentages that are listed there, but I'd also refer you to the table. But essentially it varies by - it's genetically determined and it varies by racial and ethnic group. So again, I'd refer you to the table for the specific numbers.

Dr. Douglas Throckmorton: Catherine, I think this does help make the point that I made in my comment earlier, which is it's very hard to determine exactly which child or nursing mother, specifically has this greatest risk. And that's why we've taken this broader action today.

Catherine Saint Louis: So - thanks so much. So I guess for my follow up question, I would ask, do we have any sense of whether or not the prescriptions for these two drugs to kids, is going down since your earlier actions? I mean you've already done a box warning. Did that have an effect? Do we know?

Dr. Douglas Throckmorton: Catherine, I'm going to refer you to Dr. Chai and see if she can shed some light on that question.

Dr. Grace Chai: In terms of the opiate containing products, utilization analyses are being conducted in preparation for the upcoming advisory committee Dr. Throckmorton mentioned earlier in the call. And we...

Catherine Saint Louis: I'm sorry. We can't hear you.

Sarah Peddicord: I'm sorry. Let us get her closer to the speaker.

Dr. Grace Chai: In terms of the products that we mentioned, utilization analyses are being conducted in preparation for the upcoming advisory committee meetings Dr. Throckmorton mentioned earlier in the call. We can provide a link to the website containing the materials - containing drug utilization data as well as the trends from the previous advisory committee meeting held in 2015. I think that link has been provided to everyone. The analyses are in there with the granular data providing the utilization trends up to that point.

Sarah Peddicord: Okay. Catherine, so we'll make sure we follow up with you with a link. But it is available on our website under 2015 advisory committee meetings.

Dr. Grace Chai: Yes. And in general, it looks like it is trending downwards.

Sarah Peddicord: Operator, we'll take the next question. Thank you.

Coordinator: Our next question is from Kate Sheridan with STAT News. Your line is open.

Kate Sheridan: Hi there. Thanks again for taking the time to speak with us. I was hoping you could kind of give a bit more expansion, a bit more of a sense about what actions you're considering taking for OTC codeine containing products.

Dr. Douglas Throckmorton: I'm sorry. Could you say that again? I didn't hear all of...

(Kate Sheridan): I'm wondering if you can expand a bit on what actions you're considering taking for OTC codeine containing products. Are there specific actions that are on the table?

Dr. Douglas Throckmorton: Yes. No (Kate), I don't think we've taken anything off the table as far as what we do. As you know, the regulation of over the counter products and prescription products is slightly different. And so today's action is focused on the prescription products. We're in the process of reviewing, you know, what needs to be done in the over the counter area. And, you know, as soon as we have made a decision, obviously we'd announce anything that we could.

(Kate Sheridan): Okay, great. Thank you.

Sarah Peddicord: Thanks Kate. Operator, we'll take the next question.

Coordinator: Our next question comes from Joette Giovinco with WTVT. Your line is open.

Joette Giovinco: Thank you. I just wanted to know if someone is a rapid metabolizer, what types of symptoms might they manifest if they were taking the drug? Is there ever agitation? Is it always sleepiness? And I know that you mentioned respiratory depression. And also, if someone is a rapid metabolizer of tramadol, does that automatically suggest that they will be a rapid metabolizer of codeine?

Dr. Douglas Throckmorton: I'm going to ask Dr. Racoosin to answer both of those questions.

Dr. Judy Racoosin: So the symptomatology of being an ultra rapid metabolizer results in higher levels of the opioids metabolite in the bloodstream, more quickly than

for someone who has the normal metabolism. And so the symptoms are going to be the same as respiratory depression, which is associated with any kind of opioid overdose. So that is sleepiness, that is respiratory depression, difficulty breathing. And I'm going to ask you to repeat that second question.

Dr. Douglas Throckmorton: Oh. If you had, you know, if you're at risk because of tramadol...

Dr. Judy Racoosin: So again, this is related to the cytochrome P4502D6 enzyme in the liver. And so for any drug that is broken down by that particular enzyme - so both tramadol and codeine are - have - they both - if you're an ultra rapid metabolizer of CYP2D6, you will have the same issue with tramadol and codeine. Originally, we had been working on codeine. And as we looked more into all of the data, and what other opioids might have this concern, it became clear that because the tramadol parent molecule has very little activity at the opioid receptor. But the primary metabolite has a very substantial activity at the opioid receptor that we needed to look at tramadol as well, and that's how that got included in this action.

Joette Giovinco: Can I ask one more question? As a clinician.

Sarah Peddicord: If you could follow up with us afterwards, we're trying to limit to just one question and one follow up question. But feel free to email me, Sarah Peddicord, my name is on the statement.

Joette Giovinco: Okay.

Sarah Peddicord: Thank you very much. Operator, we'll take the next question.

Coordinator: Thank you. And again, as a reminder, you can press star 1 on your phone and record your name if you have a question. Our next question is from Teresa Carr with Consumer Reports. Your line is open.

Teresa Carr: Hi. Thanks for this today. So I'm wondering - your recommendations target specific groups that are likely to be at highest risk. So, you know, children under 12, children 12 to - adolescents 12 to 18 who are overweight. Is there anything we can say to parents about these drugs for children who might not be in those high risk categories but you - they might still be concerned about these drugs when they, you know, if we were to write about this safety advisory?

Dr. Douglas Throckmorton: So just to remind you, this is all children under the age of 12. So we didn't identify any children in that population where we didn't feel like this was a concern enough to contraindicate their use. Between 12 and 18, you know, there was a group that you identified that we thought were at increased risk that also merited that same reaction - that same warning.

Are there children outside of that group that should also be concerned? I guess I'd say these are powerful medicines. I mean opioids as a class of drugs that we would hope would be used with care in all people, speaking personally. You know, I would hope that that would happen after a conversation with their health care provider. Yes, there are concerns. This is one concern that we are trying to address today. There are other concerns about the uses of opioids. They are powerful, effective medicines when used right. They can cause a lot of harm when they're not.

Teresa Carr: Okay. So I'm just wondering for - like I said, I understand it's contraindicated for children under 12. And then we'd list - you listed a couple of other specific groups for adolescents and children undergoing tonsillectomy and

adenoidectomy. So the advice is then for children that are outside of those groups, to be used with caution?

Dr. Douglas Throckmorton: Yes.

Teresa Carr: Okay. Thank you.

Sarah Peddicord: Great. Thank you. Operator, we'll take the next question.

Coordinator: Thank you. We are showing no further questions at this time. I would now like to turn the conference back to Sarah Peddicord.

Sarah Peddicord: Thank you. This concludes today's media briefing. A replay will be available in about an hour and will be available for 30 days. Please remember to check the website for the statement, the drug safety communication, which provides more about the data used to support today's action, and the consumer update. Thank you for your participation.

Coordinator: That does conclude today's conference. Thank you again for participating. You may disconnect at this time.

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