Transcript: U.S. Food and Drug Administration
Media Teleconference: FDA's Early Communication on Botox, Botox Cosmetic and Myobloc

Moderator: Sandy Walsh
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Coordinator: Welcome and thank you for standing by. At this time, all participants are in a listen-only mode.

During the question and answer session, please press Star-1 on your touchtone phone to ask a question.

Today's conference is being recorded. If you have any objections, you may disconnect at this time.

And now I'd like to turn the meeting over to Ms. Sandy Walsh. Ma'am, you may begin.

Sandy Walsh: Hi, this is Sandy Walsh with the FDA's Office of Public Affairs. I'm joined today from some representatives from our Center for Drug Evaluation and Research. Dr. Russell Katz will be our leader today.

And also he's with the Division of Neurology Products in (CDER), as well as Dr. Jane Liedtka and Dr. Jill Lindstrom from the Division of Dermatology and Dental Products.

And what we're going to do today is have Dr. Katz give you a brief overview of the announcement we made today regarding Botox and then we will take questions from credentialed media only.

And the Operator can go through that process with you on how to ask a question as soon as we get to that portion. But we'll go ahead and do a quick overview from Dr. Russell Katz.

Russell Katz: Hi. Thanks Sandy.

Yeah, I'll be very brief. I just want to say that the agency announced today that we have become aware of a number of reports of serious adverse reactions related to the use of botulinum toxin products.

And these are reactions that suggest that - that involve parts of the body and adverse reactions distant, physically distant from the site of injection. It's well known that these products can cause adverse events locally close to where the products are injected and also rarely that they have been able to cause some of these more distant side effects, including problems with breathing in certain cases.

The current labeling for these products talks about the rare potential for these distant adverse effects, including problems swallowing and problems breathing in patients with what the labeling terms underlying neuromuscular disorders.

We now believe we have reports of these distant side effects, some of which have been severe and which is- -the early communication suggests include hospitalization and death in patients without what we would call underlying neuromuscular disorders. Most of the cases that we are concerned about and

that have been serious have been cases in pediatric patients who've been treated for spasticity, usually in the lower limbs, which is an off-label use, that is to say none of the products are approved for use in children with any condition below the age of 12 and they're not approved to treat spasticity secondary to cerebral palsy.

That doesn't mean that such use, such off-label use is inappropriate. It's apparently done widely and successfully in many cases, and that's appropriate as judged by the physician community. But they are not approved for those indications.

We think that the current labeling is not as clear on this point about these distant effects in children, first of all, and in the patients without underlying neuromuscular disorders.

And - but we are continuing to evaluate these reports. We have asked the manufacturers of these drugs to submit to us their comprehensive review of their databases. We're looking at those now. And we're - so we're in the middle of trying to get a better handle on the details.

I know that a number of you are interested in the specific number of cases of deaths or hospitalization. Because this is still quite early, our - in our assessment and the numbers of cases are fluid in the sense of do we think that this case or that case is specifically related to these distant effects is still ongoing.

So we're reluctant to describe specific numbers. But we say in the early communication there have been hospitalizations. There has been at least one death attributed to these distant effects.

So I think as an overview I'll stop there and if you have any questions that I can answer, I'm happy to take them.

Sandy Walsh: Okay, Operator, we're going to go ahead and open our question and answer period for credentialed media only.

Coordinator: Thank you, Ma'am.

If anyone from the media would like to ask a question, please press Star-1. You will be prompted to record your first and last name for pronunciation purposes. To withdraw your request, you may press Star-2. Once again, if you have a question and you're from the media, press Star-1.

One moment for our first question.

Our first comes from Peggy Peck with MedPage Today.

Peggy Peck: Yes, thank you very much for taking my question.

Dr. Katz, I know you said that you don't have the exact number, but I'm wondering if you can give some sort of an estimate. Are we talking in the hundreds, in less than 100, in the thousands in terms of…

Russell Katz: (Unintelligible).

Peggy Peck: …adverse…

Russell Katz: I'm sorry, go ahead.

Peggy Peck: …in terms of adverse events?

And the other thing is I'm wondering if you can give some sense of use, practical use of Botox off-label and off-label indications, because I see often studies, as a matter of fact, in off-label indications. So my sense is that this drug is widely used for a number of indications that are not on the label.

Russell Katz: Yeah, as far as the sort of a ballpark number, it's - in terms of the specific adverse events that we're talking about, which is the - which are these what we are attributing to distant spread of the toxin, we're not talking about hundreds, not by our numbers. It's a relative handful.

But again, different people have different numbers and we're - we right now are relying on the numbers that we've generated form our Adverse Event Reporting System. The companies' numbers are probably different. Other folks might have different numbers.

But as far as these serious adverse events that we're talking about specifically today, it's a relatively small number.

Of course, we don't really know the exact number because we're relying on - when you rely on post-marketing reports, we assume that there's some underreporting of some degree or another, so we don't really know the exact number. All we know is what we have in the system.

(Unintelligible).

Peggy Peck: While not exact, would it be accurate to say less than 100?

Russell Katz: Yeah, yeah, of these specific events, yeah, in our view.

As far as the use, I can't speak to that. We have some information about usage, which is actually not releasable. So certainly it is used off-label and it's certainly used for this indication in pediatric patients off-label.

And as I say, that's perfectly appropriate if the physician believes it's appropriate. The agency doesn't typically have much to do with off-label use.

Peggy Peck: Okay, thank you.

Sandy Walsh: Okay, next question, please.

Coordinator: Our next question comes from Lynne Peterson, Trends-in-Medicine.

Lynne Peterson: I actually have two questions. Is this a response to the Public Citizen petition, number 1?

And number two, what does this mean for the cosmetic use? If you're using it in the face, is that maybe safer than if you use it in the neck?

Russell Katz: Yeah, okay, as far as it - this (unintelligible) thing a response to the citizen petition, it is not. We have been working on this for a while prior to the submission of that citizen petition, so this really in no way is in response to the citizen petition, although, of course, we're reviewing that and trying to see how this all fits together.

As far as safety in cosmetic use, again, most of the cases that we're particularly concerned about have occurred in children who have been given injections in the legs typically for spasticity for increased tone of the muscles and that we - in those cases, we believe that the toxin has spread and involved the muscles of breathing, the respiratory muscles.

There's - are some reports, a very few number of reports of these sort of distant effects with cosmetic use, but extremely rare and it's not even really clear whether or not those events could be attributed to the treatment.

It's not to say that we don't think - we don't believe it can't happen. Those doses usually of the - using the cosmetic, the doses are usually much smaller and that's not a big part of what we're seeing here.

Sandy Walsh: Okay, next question, please.

Coordinator: Our next question comes from Lisa Richwine with Reuters.

Lisa Richwine: Hi, thanks for taking my question.

My - just following up on that last point on Botox Cosmetic or do you know at - were any of the deaths in patients getting this for cosmetic use?

Russell Katz: No.

Lisa Richwine: Okay.

Russell Katz: Not that we know. But again, as I say, numbers vary depending upon who's supplying the numbers.

Lisa Richwine: Right, right. And I, you know, and I know that you've already addressed this issue of the numbers, but if I could bring it up again and mention that Public Citizen had said 16 deaths. I mean, is that in the ballpark of what you've seen?

Russell Katz: Again, let me (unintelligible)…

Lisa Richwine: Because it - without your number, then we're forced to use their number, so.

Russell Katz: Yeah, I don't want to speak specifically to the numbers. The only thing I would say about deaths or the reports of any specific adverse events that we obtain from a post-marketing setting depend - there are more or less deaths depending upon what you're talking about.

Lisa Richwine: Okay.

Russell Katz: It's - what we're particularly interested in is whether or not there have been deaths or serious reactions related to this distant spread…

Lisa Richwine: Okay.

Russell Katz: …which looks a lot like naturally -- if I can use that word occurring -- botulism.

Lisa Richwine: Okay.

Russell Katz: There may be deaths reported.

Lisa Richwine: Okay, yeah.

Russell Katz: (But they) may be due to completely different reasons.

Lisa Richwine: Right, yeah. And, you know, we're interested in…

Russell Katz: (Unintelligible) populations, particularly the pediatric population of cerebral palsy are - can be quite sick. And so…

Lisa Richwine: Mm-hmm.

Russell Katz: …bad things happen to those kids naturally unfortunately. So it's a question of numbers of deaths related to this event or numbers that we think are related to this event or numbers of deaths that are in our system just in total. (Unintelligible)…

Lisa Richwine: Yeah, no, I think we'd all like to know, you know, the ones you think might be related.

Russell Katz: Yeah, very, very few. Very few. But again, we're still in the middle of looking at this in detail.

Lisa Richwine: Okay. You said I think a relative handful of deaths?

Russell Katz: A relative handful of any of these serious reactions, including hospitalization and death.

Lisa Richwine: Okay, thank you.

Sandy Walsh: Next question, please.

Coordinator: The next question comes from Jennifer Smith from FDA Week.

Jennifer Smith: Hi Doctor. I just want to touch - I just want to confirm again when you mentioned about the inadequate labeling right now, the (unintelligible) if you can just go over that labeling component again, as well as now Public Citizen has asked (you then therefore) for a Black Box on these Myoblocs and for

these Botox products. So I'm wondering if that's a consideration FDA has if the labeling is not sufficient?

Russell Katz: Yeah, the current labeling has in the warning section a statement about rare occurrence of these distant or systemic effects in patients with underlying neuromuscular disorder.

Jennifer Smith: Okay.

Russell Katz: And it's not as - and they describe what those disorders are, at least examples of those disorders.

Most people in the field would not consider spasticity due to cerebral palsy as strictly speaking a neuromuscular disorder.

Jennifer Smith: Okay.

Russell Katz: And it's not one of the examples that are given in current labeling. So now again we have cases which we think are attributable to the treatment in pediatric patients in particular with cerebral palsy and spasticity.

Jennifer Smith: Okay.

Russell Katz: So we don't think that's a neuromuscular disorder as that term is commonly understood…

Jennifer Smith: Okay.

Russell Katz: …by physicians. So in that sense, the current labeling doesn't really describe cases of this sort that we now believe we have. So that's why we're looking obviously at potentially changing labeling.

Jennifer Smith: Right.

Russell Katz: As far as what the new labeling will be, whether there will be a box warning, well - it's too early to tell. We are certainly consider every option. It's certainly not - it's certainly also not the case generally speaking that all significant adverse events end up in a box warning. There are many considerations that go into where in labeling we put something and…

Jennifer Smith: Right.

Russell Katz: …how we say it in labeling. So it's a possibility, sure. It's certainly something to be considered. But it's too premature to say anything definitive about that.

Jennifer Smith: Okay, thank you.

Sandy Walsh: Next question, please.

Coordinator: Lauran Neergaard from the Associated Press, your line's open.

Lauran Neergaard: Oh, hi, Dr. Katz.

I'm wondering I guess what has changed to make this become an issue now because it's something that the agency has been aware of for quite some time. I'm - I have in front of me (unintelligible) report authored by FDA people published in the Journal of the American Academy of Dermatology that talked about 28 deaths, many of them this type, including adults. And today's

statement makes it sound like it's a handful of kids, that it's a brand new thing. So can you go (unintelligible)…

Russell Katz: Well, I don't think that - I'm sorry, go ahead.

Lauran Neergaard: …go into a little more for me exactly what's changed and talk with me a little bit, too, about those previous descriptions of the adult deaths that they were, you know, maybe ruled out or something.

Russell Katz: Well, again, as I say, there's - trying to assess causality or mechanism of death from post-marketing reports can be tricky. I think what's new is that we think that in people who do not have these underlying neuromuscular conditions or diseases, we believe we now have documented cases of what presumably is distance spread or certainly systemic adverse events and now in particular in pediatric patients.

But I think that's what's new. And that's why we're announcing it. As I said, the labeling currently says it - this can happen rarely in patients with underlying neuromuscular disease. We think we now anyway have evidence that it can happen in a broader population.

Still, again, by our numbers, I think quite rare, but nonetheless…

Lauran Neergaard: Can you talk about dosing?

Russell Katz: …I think - excuse me?

Lauran Neergaard: Can you talk about dosing? I mean, is the dosing (unintelligible)…

Russell Katz: The only thing I can say about dosing is what's in the early communication and that's - and it's been seen in a wide range of doses. We've seen some of these significant adverse events at doses that people presumably believe are the appropriate doses for this condition and cases of doses which are considered to be higher.

Now again I have to say that none of these products are approved for this use. I'm talking specifically about the spasticity and cerebral palsy in pediatric patients, so none of them are approved for that use.

So we, of course, can not endorse any particular dosing regimen for this. No dosing regimen to the best of our knowledge has been shown to be safe and effective.

Again, that does not mean that it's inappropriate to use it off-label in this way. But it - and there are guidelines I gather for dosing this population off-label. And as I say, some of these cases presumably occurred with doses that conform to those guidelines and some were at higher doses.

Sandy Walsh: Okay, next question, please.

Coordinator: Alicia Ault with Skin & Allergy News.

Alicia Ault: Yes, thank you for taking my question.

Most of my questions have actually been answered, but just on that last point about the dosing and whether this is - it looks like the botulism cases were not just in pediatric, not just in kids, but also in adults. So I'm wondering what conditions did those adults have? What were they receiving the injections for? Is it a variety of illnesses or…?

Russell Katz: Well, I think were some were on-label. Some were sort of just general muscle spasm. It's - of course, the information from these reports is often incomplete, so it's difficult to tell in many cases exactly what they were getting it for.

Alicia Ault: So you don't have any kind of clue as to this is only affecting people with spasticity or you just have no idea…

Russell Katz: No, but I think mostly - and again, it depends what you mean by spasticity, but I think mostly the drugs are used in people who have spasm of muscles or spasticity, which are actually two different things.

But they both result in what we would say is increased tone of the muscle that someone wants to relax regardless of why that tone is increased, so - and so they have normal contraction of the muscle. So mostly they're used for those sorts of things in various parts of the body.

Alicia Ault: But it sounds like you can't rule out that any of these were in cases where the Botox might've been used for cosmetic purposes.

Russell Katz: I think we think as far as these distant effects, what we called systemic effects, I think we think that we might have a case or two. But that - and even those are difficult to attribute to the drug.

So there's very few as far as we know from our database at the moment, again, given our preliminary look at this that are attributed to the cosmetic use. But we don't rule out the possibility that it might happen with that use, although we think the real message today is particularly in pediatric patients with spasticity, which is really what we think is new, at least with regard to labeling.

So is it possible with cosmetic use? Possibly. But is that - very unusual.

Alicia Ault: All right, thank you.

Sandy Walsh: Next question, please.

Coordinator: (Jennifer King) from Associated Press, your line's open.

(Jennifer King): My question's been answered. Thanks.

Sandy Walsh: Great. Thanks. Next question, please.

Coordinator: (Meg Tuey) with The Chicago Tribune.

(Meg Tuey): Yes, thanks for taking my question.

I was wondering what an - what we know about whether or not the injections have caused severe, you know, illness or death for people - anybody who's gotten injected, had the Botox injected in their vocal cords for spasmodic dysphonia?

Russell Katz: Yeah, by our numbers no, we don't have any reports of that.

(Meg Tuey): Okay.

Within this particular like dataset or period?

Russell Katz: I'm sorry, I didn't hear the beginning.

(Meg Tuey): Within this specific dataset or period?

Russell Katz: (Unintelligible) the post-marketing data reported to the FDA is the dataset that we looked at here.

(Meg Tuey): Okay.

Russell Katz: In addition to the literature, but that's where most of this information comes from.

(Meg Tuey): Mm-hmm. Okay, thanks.

Sandy Walsh: Great. Next question, please.

Coordinator: (Unintelligible) CNN. Amy Burkholder with CNN, your line's open.

Amy Burkholder: Yes, hello, thank you.

We actually have two questions. And my first one is, you make it clear that this appears to be an issue with dosing and not bad Botox. Can you tell us how you know that it's not the Botox itself?

And our second question is this, and you partially answered it -- talking to the American Academy of Neurology, we know that Botox is used very widely and in very young kids for cerebral palsy.

But that raises a whole question, you know, they could be using it very early and at what dose. Obviously that's not something you regulate, but could you address that?

Russell Katz: The first question had to do with how we know it's not bad Botox. I think we think that the - that there's absolutely no evidence for that from any other report or any other angle.

We think that we understand the mechanism of these serious adverse events, which we think is related to spread of the toxin from the local tissue where it's injected to more distant sites like the muscles of breathing.

So we think we understand very well how these products work from therapeutic point of view and the mechanism for the adverse event. So my point being these events are - we think, anyway, understandable from the point of view of the pharmacology of the drug and how the drug works and how the body responds to it.

So it is perfectly consistent with what we think the drug is capable of doing. And so we think we understand this. And there's no reason to believe that it's related to bad Botox.

And I'm not even sure exactly what bad Botox means and what it would result in clinically if someone was injected with it. So we just think this is sort of consistent with what we know about the drug. So I think that's why we're not worried about that.

The second question had to do with the dosing in young kids. I can't really speak to that. As I say and as you reiterated, we don't know what the right doses in these cases.

We haven't approved the use of these products at any dosed in this population, so it's hard for us to comment on what the right dose ought to be or, you know, or what people are even doing out there.

Sandy Walsh: Okay, next question, please.

Coordinator: Jacob Goldstein with Wall Street Journal, you may ask your question.

Jacob Goldstein: Thanks.

So does this early communication have any bearing at all on how physicians and patients should think about the cosmetic use of Botox?

Russell Katz: I - you know, that's - we put the information out there for people to make their own personal best judgment about this. We have seen cases of something that looked like this with cosmetic use, very rare. I think people should be aware that there's the potential for this to happen.

People presumably have different sensitivities to various doses. And so people should be on the lookout for it. And if somebody does use it cosmetically and they subsequently develop symptoms that might be related to this distant spread, then I think both patients and physicians should take those symptoms seriously and think about this as a possibility.

Jacob Goldstein: And should this be - I mean, is there a - is the potential risk of these distant effects high enough that it should be considered as part of the risk/benefit analysis of somebody who's considering whether to get a cosmetic Botox treatment? Or is it so low as to be essentially a nonentity?

Russell Katz: We're in the - as I have said before, we're in the process, the relatively early stages of looking at all of the data in great detail. So it's hard to say. Right now given the number of cases we have in-hand, we think it's probably quite

rare given the number of reports we have and the apparently very large use for this indication.

So right now, it's - we think it's quite rare. But again, time will tell as we continue to review this.

I think the main thing, again, from the cosmetic use is that people should be aware that this is a possibility, however rare, and that if they do develop these symptoms, they should take note of them.

Jacob Goldstein: Thank you.

Sandy Walsh: Great. Next question, please.

Coordinator: Our next question comes from Anna Mathews with The Wall Street Journal.

Anna Mathews: Hey, sorry there are so many of us.

Just briefly, you said I think there were only one or two cases that may have been associated with cosmetic use and none of them deaths. Were there any hospitalizations that were possibly associated with cosmetic use? I'm assuming not, but…

Russell Katz: I have to check.

Marketed product, I'm not sure there was - yeah, actually there was at least one hospitalization, but again, it was questionable as to whether that was related to the treatment or whether it was related to some other cause. But there was at least one hospitalization.

Anna Mathews: With someone getting Botox Cosmetic?

Russell Katz: Yeah, right.

Anna Mathews: At least one hospitalization.

Sandy Walsh: Can you (unintelligible) Anna?

Anna Mathews: Yeah?

Sandy Walsh: We - we're going to just put you on hold - everybody on hold for one second and one of our dermatology experts is going to give us some advice on this.

Okay, we got a clarification.

Russell Katz: Hi. Yeah, right, right, let me clarify it. They got a Botox for a cosmetic indication, but not Botox Cosmetic.

Sandy Walsh: Does that make sense?

Russell Katz: Because those are two different - Botox and Botox Cosmetic are different products.

Anna Mathews: Okay, so there was at least one hospitalization…

Russell Katz: (Different labels).

Anna Mathews: …from someone who got Botox, not Botox Cosmetic, but Botox, but…

Russell Katz: (Unintelligible).]

Anna Mathews: …got the Botox for a cosmetic use.

Russell Katz: Right.

Anna Mathews: Do you know what use then?

Russell Katz: For - yeah, for glabellar, which is, you know, these frown lines between the eyebrows, which is - it's approved.

Anna Mathews: Okay.

And again, it was actually Botox, not Botox Cosmetic?

Russell Katz: Correct. That's the best information we have.

Anna Mathews: Okay.

Anything else you could tell us about that case, although forgive me, I understand it is just one case.

Russell Katz: No, I don't to really go into the details of the case. But it ended with weakness and hospitalization, although as they say, it's not entirely clear that it was treatment-related. Possible it was.

Sandy Walsh: Great. Next question, please.

Coordinator: Mike Huckman with CNBC, your line's open.

Mike Huckman: Thank you.

I'm just wondering if this is the reason or one of the reasons why there's a delay in the approval of Reloxin? Of it isn't, if it could mean a further delay for that?

And then separately, if you would please go down the list of symptoms and problems in layman's terms of what people should look for exactly?

Thanks.

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Russell Katz: Yeah, I can't speak at all to what effect this - our consideration of this issue might have on some pending application. So I certainly - I can't speak to that at all.

I think what we're mostly worried about is - and it's actually, I mean, the main ones are listed in the early communication. What called - well, difficulty swallowing, which is known as dysphasia, change in voice, a generalized weakness and most particularly shortness of breath or difficulty breathing.

There are other signs, but those are the ones that we list here and those are the ones that (unintelligible) - and again, depending upon where the drug is injected, and again, we're talking here mostly today about these distance effects, the effects in muscles that are quite distant from where the injection is.

If you get injected in the legs and the eyelids start to droop or your head becomes difficult to lift, anything that - or weakness - a symptom where it's attributable to muscular weakness distant from where the injection was, those are things that people should watch for.

Mike Huckman: Thank you.

Sandy Walsh: Great. Are there any more questions?

Coordinator: Ma’am, at this time, we have no further questions.

Sandy Walsh: If there anyone that would like to ask a question, please hit is it star-0? Star-1?

Coordinator: Star-1, Ma’am, yes.

Sandy Walsh: Okay, Star-1.

Okay, if there's no further questions, that will end our call today. If you have any further questions, please call the FDA Press Office at 301-827-6242 or you can email me. This is Sandy Walsh at sandy.walsh@fda.hhs.gov.

Thank you.

Coordinator: Thank you for participating in today’s conference call. You disconnect at this time.

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