Media Briefing on FDA's Request for the Removal of All Ranitidine Products (Zantac) from the Market

Moderator: Sarah Peddicord
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Coordinator: Welcome and thank you for standing by. Today's conference is now being recorded. If you have any objections, you may disconnect at this time. All participants are in listen-only mode until the question and answer session of today's conference. At that time, if you'd like to ask a question, please press star, then "one." I will now turn the conference over to Sarah Peddicord. Thank you, ma'am. You may begin.

Sarah Peddicord: Thank you, Karen. 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 that it has requested a withdrawal of all ranitidine products, commonly known by the brand name Zantac, from the U.S. market.

By now, the press release on this announcement has been issued and is available on our website. Dr. Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, will provide some brief remarks to go over the specifics of today's announcement. We will then 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. I will now turn the call over to Dr. Woodcock.

Dr. Janet Woodcock: Thanks Sarah, and hello everyone. Assuring the quality and safety of the drug products that Americans take every day is one of our greatest responsibilities. We've been investigating the detection of the contaminant known as NDMA in ranitidine medications with the brand name of Zantac, that are approved to treat heartburn and other conditions. Before I go into the

details of today's announcement, I want to give some history of what's been going on with this particular issue.

Our discovery of NDMA in ranitidine was part of a broader investigation into nitrosamine impurities that began with finding nitrosamine in generic blood pressure and heart failure medicines known as ARBs; ARBs include medications like valsartan and losartan. We were deeply concerned when we learned about the presence of these impurities and we immediately undertook a major operation to investigate and identify the root causes for their presence in some of the ARB drugs, and to work with companies to address the risks that the impurities could pose to patients.

Now, our ongoing effort there determined that the impurities in ARBs may be generated by specific chemical reactions when making the drugs' API, or active pharmaceutical ingredients, and some of these chemical reactions may have involved impurities that were in some of the reagents or solvents that were used in the manufacture. Our scientists had to develop very novel and sophisticated testing methods that were specifically designed to detect and measure the nitrosamine impurities in each one of the different medications that we were testing and we collaborated closely with the international regulatory agencies and with the industry, sharing these methods and the test results, to protect Americans who were taking these products.

As a result, ARB medicines have been recalled lot by lot when testing revealed potentially unacceptable levels of nitrosamine, including NDMA and others. But this then raises the question - what about other drugs with a similar manufacturing process, or other similar chemical liabilities? And we developed a sophisticated and large-scale model of which drugs might be at risk for developing the impurities during manufacturing and we're continuing to look at those now in partnership with the international regulatory and

industry, because there are a large number of drugs and we need to cover them all as quickly as possible.

Fortunately, the FDA maintains one of the most advanced pharmaceutical laboratories of any regulatory agency in the world and we have an aggressive and comprehensive testing program. To date, no new drugs have been found with concerning levels of nitrosamine formed during the manufacturing and if we do identify them, we will take swift action to tell the public and remove them from the market. I want to continue to emphasize because I know many of you have got questions about this - overall, the risk to individual patients potentially exposed to nitrosamine in any drug product remains very small. This doesn't diminish the significance of this issue or our concern because there should be acceptable levels only within drug products.

Now, that story brings us back to ranitidine. The impurity, NDMA, that we found in some ranitidine products last year, comes in a different way than what we've seen in the blood pressure medicines. With ranitidine, the NDMA is not purely formed during manufacturing, but instead appears over time in storage, especially when stored at higher than room temperatures, and could ultimately result in the tablets having unacceptable levels of this impurity and people being exposed to higher levels than we consider acceptable.

We've communicated quickly with the public upon finding this new source of NDMA and we released our testing results in November last year and our testing of ranitidine products has been very robust from samples of prescription and over the counter products, including prescription syrup used for infants. The FDA has already worked with the affected companies to remove ranitidine products that by testing were found to have unacceptable levels of NDMA and they've been taken off the market previously, but there are still questions about how the impurity is formed in ranitidine over time

during storage, for example, what impacted the drug packaging in the development or the formulation - the specific formulation with the development of NDMA.

This presence of NDMA in ranitidine that occurs over time may be a fixable problem and we're open to companies demonstrating that their product, they reformulated their product, or have a way that is stable. So, today's action requesting companies to withdraw all remaining ranitidine products from the U.S. market has been taken out of an abundance of caution, even though these products, when they come off the factory line, they don't contain unacceptable levels of ranitidine. We don't know, if they are stored under various conditions, what might end up at the end of the day after long-term storage.

Patients should be advised there are alternative prescription and over the counter medicines available to treat their condition and that's also on our website, and of course many, many people have already switched when much of this information came out earlier, and many of the drugs have been pulled off the drugstore shelves in the past.

Now, we're also aware of other drugs that have been discussed in the international community as a cause for concern for having or developing nitrosamines, and we do want to assure the American public we've done testing across all potentially impacted drugs that have been mentioned and we'll notify the public if we observe any unacceptable levels of nitrosamines in the U.S. drug supply chain, and those medicine lots or medications will come off the market in the U.S. But, more broadly, our overall response will include issuing guidance soon on steps all drug manufacturers should be taking to detect these types of impurities, including a risk assessment, like a chemical risk assessment to look at what is the probability of generating them, and then testing as a routine matter.

We will continue to improve our science and the standards for detecting and preventing these risks and we're going to keep the public informed of our ongoing process and as always, our goal is to ensure that safe, effective and high quality drugs remain available for the American public and those that are not, are not available to the public. Thank you.

Sarah Peddicord: Thank you, Dr. Woodcock. At this time, we will begin the question and answer portion of our call. When asking a question, please remember to state your name and affiliation. Also, please limit yourself to one question and one follow-up so that we can get to as many questions as possible. As a reminder, this media call is about today's announcement and we will only answer questions related to the market removal request at this time. Karen, we will take the first question, please.

Coordinator: Thank you. Our first question comes from Amy Birnbaum from CBS Evening News, your line is now open.

Amy Birnbaum: Hi, thank you for taking my call on this news conference. Could you describe a little bit about the levels that you've found during storage, you know, room temperatures and a little bit about whether it was, the levels increased with higher temperatures? Thank you.

Dr. Janet Woodcock:

Certainly, yes, especially with extremely high temperatures, which you wouldn't find the product stored at and we'd hope you don't put your drugs in the oven. That would rapidly accelerate the generation of NDMA but the level is really dependent on the formulation in the specific product, but yes, they did increase over time and sometimes they increased above what would be considered an acceptable level after storage, especially with elevated

temperatures. But we saw, at regular room temperatures, we saw increases over time there too, although generally those stayed below the acceptable level.

Amy Birnbaum: Thank you, Dr. Woodcock.

Dr. Janet Woodcock: Sure.

Sarah Peddicord: Amy, any follow-up questions?

Amy Birnbaum: Just what kind of testing has been done to detect for the presence of ranitidine in the body. I know you were starting to look at that. Anything new to look forward on that?

Dr. Janet Woodcock: Yeah, it has to be done in a clinical trial and we are undertaking that, but it hasn't been finished, so as soon as we have results, we'll let people know.

Amy Birnbaum: Thank you.

Dr. Janet Woodcock: Sure.

Coordinator: Thank you, as a reminder please press star then “1” if you'd like to ask a question. Again, please press star, then “1” at this time if you'd like to ask a question. Please be reminded to report your first and last name as well as your affiliation. Our next question comes from Leigh Boerner, Chemical Engineering News, your line is now open.

Leigh Boerner: Hi, so my question, you said earlier that the levels of NDMA depend on the formulation and the specific products. Could you give a range of the levels of NDMA that have been found in ranitidine products?

Dr. Janet Woodcock: I'm sorry, I can't off-hand. Most of them were well below our threshold for acceptable levels and that's why we haven't pulled ranitidine off the market, but particularly when they're stored under heat, then they generate nitrosamines or NDMA. I don't have the actual numbers and it does vary. It is very specific to different formulations.

Leigh Boerner: Is the FDA going to be making that information public?

Dr. Janet Woodcock: I don't know. I think our testing wasn't totally comprehensive, so we'll have to see how much we'll make available.

Sarah Peddicord: Thank you. We'll take the next question.

Coordinator: Our next question comes from Malcom Spicer, Informa; your line is open.

Malcolm: Thank you so much. Good day, everybody. Dr. Woodcock, a couple of questions real quickly, this doesn't withdraw approval for ranitidine in any product it is actually being used in already, just an FDA request that they are withdrawn from the market?

Dr. Janet Woodcock: Yeah, thank you for asking that question. Let me clarify for everyone on the line. This is different from-first of all, FDA doesn't have mandatory recall authority, so we call for voluntary actions by manufacturers and sometimes they don't agree and we have to go through an administrative process. This is a market withdrawal. Okay? It is not a recall, because technically the products are okay. They've met all their specs and so forth. It's only when they are subjected generally to heat stress do they manifest higher levels, and that isn't what we'd expect that these products would be stored under higher temperatures.

So, they meet, technically, all their stability requirements and so forth, but clearly we can't have products on the market that if they are stored under conditions consumers might store them under, right, that they would become unacceptable. And so, what we're asking the manufacturers, I'm not saying they should withdraw their applications or approvals. We're not doing that. We're saying to pull this product, your products, off the market, off the shelves. We're telling consumers they should pitch them, and then if they want, they can generate the scientific data or reformulate their product, or in some cases, establish cold chain if that's what they want to do, for some of the prescription ones that would render them stable, and if they could prove that, then that would be completely acceptable. But I said as they come off the manufacturing line, they don't have excessive NDMA in them (unintelligible).

Malcolm: Yes, ma'am, thanks very much for that. A follow up would be, if I may please, would you recall other than the other nitrosamine ingredients or other drugs that had been recently found to be potentially susceptible to nitrosamine contamination, is there a precedent, or if not a precedent, an event to happen like this, particularly in the OTC sector that comes to mind?

Dr. Janet Woodcock: No, not really. I mean, heparin contamination, we had to get the heparin products that had excessive levels of over-sulfate and chondroitin sulfate, we had to get them off of the market, right? They were contaminated. And that case was different than this case. That was a recall because they were actually defective. Here we're saying they aren't defective, but they could become defective if they were stored under special conditions for the product. So, I can't recall anything exactly like this before.

Malcolm: If I may, one more question, I sense that you have got indications from the industry that cooperation agreement with this request from FDA is universal?

Dr. Janet Woodcock: Yeah, usually we do because if we say there could be a safety signal with their product, and usually the liability concerns would overweigh any other concerns for the manufacturer, so usually we get full cooperation when we call for a market withdrawal or a recall.

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

Coordinator: Thank you. Our next question comes from Ed Silverman of STAT News, your line is open.

Ed Silverman: Hi, thanks for taking the question. Hi Janet.

Dr. Janet Woodcock: Hi.

Ed Silverman: Could you address just more specifically concerns about metformin and if there's any timeline to address that? Because I know it's been kicking around for several weeks already and it's sort of under the same umbrella that you mentioned with the blood pressure drugs and now ranitidine.

Dr. Janet Woodcock: Sure, well, some regulatory agencies in the world for products that are in their market have found elevated levels, but we've tested a lot of metformin and we haven't found any product in the United States with elevated, unacceptable levels of NDMA or other nitrosamines.

Ed Silverman: So is that the end of it or will there be further testing? Because I know there was a petition filed by the same company that field a petition with ranitidine six or so months ago, so I mean does that indicate that there's no further need to this or is that still sort of an open book?

Dr. Janet Woodcock: No, I mean, we looked, okay, we have verified that we don't think there's any immediate cause for alarm with metformin. We're moving ahead with having the whole industry do risk assessments and then initiate testing, and I think we'll probably be doing that with worldwide regulatory agencies, so that'll become a new standard, so this needs to be institutionalized, put into the ordinary, proactively into the ordinary testing of pharmaceuticals so we don't find out once they're on the market that there's a problem.

Coordinator: Thank you. Our next question comes from Donna Young of S&P Global News, ma'am, your line is now open.

Donna Young: Thank you. Thank you, Dr. Woodcock for taking my question. I wanted to have you respond a little bit about the long term use mostly like in infants, since that drug is available in that age group and kind of what advice you're giving parents at this point that did use it for several months, and what the FDA is doing to maybe track that in that population? Thank you.

Dr. Janet Woodcock: Right, well, as we said, we don't feel there is a significant risk to any individual, including infants, who are taking the syrup, okay, and if we did, we would take more action but we do not think there is risk for nitrosamine estimated over lifetime exposures to certain levels, but we understand the use for reflux in infants and that's been going on a long time. We don't think that raises the risk for individual infants and we don't think consumers should be concerned about that.

Coordinator: Thank you, our next question comes from Gina Yu of CNN, ma'am, your line is now open.

Gina Yu: Hello?

Dr. Janet Woodcock: Yes.

Gina Yu: Oh hi, great, yeah, thanks for taking my call. So I just wanted to confirm, were there are any other drugs that could contain the NDMA and also what other tests are being done, you had talked about metformin, what other drugs are currently being investigated and tested?

Dr. Janet Woodcock: We have a whole long list, all right, and we don't, I mean, there are many ways nitrosamines can get into a drug product. It could be formulation, not the active ingredients, it could be packaging, and so what we're doing is going to be putting out, fairly soon, guidance to industry in how we want them to proactively look at this, so that then all drugs can have a risk assessment and the ones that are worrisome could all be tested.

Now, test methods have to be developed for each one of these products. You can't just use the same test on all the different products. So, there's a lot of work to be done. But to your question, we've taken the highest risk ones, and we've tested them, and we haven't made any more announcements. We haven't found unwarranted levels of nitrosamines in any other products that we've tested.

Gina Yu: Could you explain what the highest risk ones are?

Dr. Janet Woodcock: Well, not without a Ph.D. in organic chemistry, you know, they have to have certain nitrogen bonds within their chemical structure, or there are certain ways the synthesis is being done that might generate the nitrosamines during the synthesis, so the organic chemists have to look at these reactions. Our guidance should have more information on that. However, I doubt it's going to be very accessible to the average reader.

Gina Yu: Yeah, sure, could you at least list what the highest ones were besides ranitidine?

Dr. Janet Woodcock: You mean highest risk?

Gina Yu: Yes. You had mentioned that you looked into other highest risk ones but didn't make any announcements because you didn't find any, what were the other highest risks for having NDMA?

Dr. Janet Woodcock: Sorry, I don't have that information on hand right now. But they may not have been the highest risk. They were what our risk assessment generated as high risk products, or like in metformin, where some other group felt there was a problem, so if we get reports like that, we'll test that drug.

Gina Yu: Okay, thank you.

Dr. Janet Woodcock: Sure.

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

Coordinator: Thank you. Our next question comes from Dela Taghipour of ABC News. Ma'am, your line is now open.

Dela Taghipour: Hi, thank you so much for taking my question. We understand that this is a really important, not recall, but withdrawal, but we're wondering, it has taken several months since the first reports of independent labs reporting concerns. It's been nearly six months and so just trying to gauge what maybe caused the delay in the announcement? Thank you.

Dr. Janet Woodcock: Sure, well, we did testing when we heard, got reports that ranitidine had some NDMA in it, right? Those were the first reports. We did not have the same findings. In fact, our findings were really, really different than what was reported, all right, and our findings were verified by other regulatory labs around the world. So, then we got reports, of course, as someone else mentioned that ranitidine was perhaps modified in the human body. Pharmacologists are quite skeptical of that.

However, we have set up a human trial to look at that, okay, so that's another different way people might be exposed to nitrosamines from ranitidine, and then there were reports that ranitidine was unstable upon storage, all right, and upon heat stress, and some of those we repeated that. That takes a while because you have to store them, right? We got drugstore samples and everything and they were fine, right? So, we did that experiment. We had to do an experiment where we stored them over time and looked at how the levels changed and then we found, especially with high heat, with moderate heat, sometimes the levels will get up above what is acceptable, and at room temperature, generally the levels accumulate over time, so if somebody keeps their ranitidine around for well past the dating period, we thought they perhaps would be exposed to more ranitidine than is acceptable.

So, that's where we are today. We've completed those stability studies, and heat studies, and different conditions. Our conclusion is that the ranitidine on the market is acceptable, what we have tested, the levels are acceptable, but upon storage, they increase and therefore, that's why we're conducting this market, asking this market withdrawal be done.

Dela Taghipour: Thank you so much.

Sarah Peddicord: Thank you, and Karen, I think we have time for one more question on today's call.

Coordinator: Thank you. Our last question will come from Amy Birnbaum of CBS Evening News, your line is now open.

Amy Birnbaum: Hi, thank you. I just wanted to get an estimate if you know, since so many had already withdrawn ranitidine and Zantac, all that, what percentage of product might be left on the shelves?

Dr. Janet Woodcock: That's really hard for us to say. We're also advising patients and consumers to switch and discard their existing supply so there might be more out there in the hands of people in their kitchen drawers, but we don't know how much that is. I agree, most of particularly over the counter has been withdrawn, has not been available for some time, and that made us quite comfortable while we were doing our analyses. Probably, some of the prescription forms are still available, so that's a change there. That includes the infant syrup and some prescription ranitidine.

Amy Birnbaum: Thank you.

Dr. Janet Woodcock: Sure.

Sarah Peddicord: Great. Thank you so much everyone. 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 press release and my contact information if you need to follow up with any questions. Thank you for your participation. Take care.

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