FDA MEDIA BRIEFING ON HEPARIN

Moderator: Karen Riley
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Coordinator: Good afternoon and thanks for standing by. At this time all participants are in a listen only mode. After the presentation we will conduct a question and answer session.

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

Now I would like to introduce your host for today's conference Miss Karen Riley with the Office of Public Affairs with the FDA. You may begin.

Karen Riley: Thank you. Welcome to today's media call. We're here today to provide you with an update on FDA's ongoing heparin investigation. With me on the call today is Dr. Janet Woodcock, director of FDA Center for Drug Evaluation and Research.

She will provide an opening statement then we will go to Qs and As. Before we start today's discussion let me remind people that today's call is for credentialed media only.

So, we have a lot to say and so let's get started. Dr. Woodcock.

Janet Woodcock: Thank you. The purpose of this call is to update you on the progress of our work on the problem of heparin contaminated with oversulfated chondroitin sulfate or as we call it OSCS that has been associated with serious adverse events.

As you know because there is no routine method to test for this contaminant, FDA developed analytical methods for testing heparin active pharmaceutical ingredients which we've posted on our website on March 6th.

On March 12th we followed up with a request that US manufacturers and suppliers test all lots of heparin API. We encouraged regulators worldwide to check their supplies with these new test methodologies and provide a contact for regulators and manufacturers to update us on their results.

Many regulators and manufacturers have done so. What we've found is that contamination of the heparin supply is a worldwide problem. Contaminated heparin has now been found in some lots of heparin in at least ten [plus U.S.] countries, and we're posting a map that will show which country - in which countries this has been found.

These findings of contamination are leading to quarantines and ongoing recalls of the affected products in many parts of the world. The contamination has been detected in API lots that were manufactured at least as early as 2006.

Because of the time frame for manufacturing final heparin dosage forms from API, the contaminated heparin generally entered the worldwide market in 2007.

It found its way into drug products, IV flush products, medical devices, and possibly in vitro diagnostic tests. All of these products are being tracked down and evaluated by regulators and manufacturers.

At the present time to our knowledge, adverse events have been reported only when patients received a large bolus dose intravenously. We do not know where the contamination occurred.

However we do know that the contaminated products used product from API and crude heparin companies across a broad area of China. Additionally we now know of at least ten Chinese firms that are in the supply chain for contaminated heparin.

We also requested manufacturers of another form of heparin, low molecular weight or fractionated heparin, to test their products and API. That's because they use heparin as the source of low molecular weight heparin.

Testing of these products by various manufacturers has also revealed some contamination by oversulfated chondroitin sulfate. Regulators in various countries are evaluating the low molecular weight heparin situation in their area. And we discussed this at the regulator's meeting that I'm going to talk about in a minute and arrived at a consensus about the approaches.

Low molecular weight heparin is generally used for a short period of time for blood thinning or anti-coagulation to prevent blood clots from forming in the veins or preventing extension of blood clots that are already formed.

I'd like to stress for US health care practitioners and patients that fractionated heparin currently on the US market with a trade name of Lovenox and others has been tested and is free of contaminant.

We will continue to provide to you complete information on the status of heparin supplies in the US.

Because of the scope of this problem that was revealed by the testing, FDA held a meeting on April 17th and 18th with international regulators representing more than ten countries.

The Chinese SFDA and Chinese scientists attended. The USP and the European pharmacopeias participated and we also had several academic heparin experts.

The goals of the meeting were to discuss the analytical testing results related to the worldwide heparin supply and to share inspectional issues and findings.

Now we had two days of meetings but a brief summary is that the testing discussion revealed that we found only one contaminant, something that should have been there was identified in the samples tested and that was the oversulfated chondroitin sulfate.

So that was identified as - it was the same contaminant. The proton NMR and the CE methods posted by FDA were successfully used around the world.

The analytical scientist identified a need for more well-developed screening methods and confirmatory and quantitative methods generally.

And that means we need a screening method that is easy to use and can be put into place routinely, and also, if we find anything, we need methods where we can then identify and find out how much is there.

There was agreement on the need to update the compendial testing method. These are for example what the USP uses and others that is required for heparin to be tested.

USP and the European pharmacopeias have agreed to collaborate to rapidly incorporate testing relevant to oversulfated chondroitin sulfate in the short term but also to develop more comprehensive methods for demonstrating purity over the long term.

So these methods will be modernized. Testing also revealed in some of the samples an excess level of a known heparin impurity, dermatan sulfate in a number of samples.

Because of this it was agreed there should be a public standard for dermatan sulfate content. As you know heparin is derived from the intestines of pigs and dermatan sulfate is a byproduct of this process.

But the amount of dermatan sulfate in some of the samples was in excess of what we would expect significantly for a byproduct.

Also in the regulator's meeting there was a discussion of the low molecular weight heparin findings and as I said general agreement on how to approach low molecular weight heparin.

For the - we also had inspectional discussions about the inspectional results. We agreed - we have an international rapid alert notification system, and this has worked very well in this crisis.

And the international regulators agreed to utilize and enhance this notification system. The heparin problem generally illustrated the need for us to focus on enhanced regulation and scrutiny of the whole supply chain for drugs, including all sources of materials, including the natural sources.

And the regulators agreed to hold an inspection summit in 2009 to apply lessons learned from the heparin situation, particularly on how regulators worldwide can continue to build on existing collaboration.

The Therapeutic Goods Administration of Australia or TGA will lead the organization of the summit and FDA will host the summit.

And the list of invitees to this inspection summit will be much broader than the folks who were at the heparin focus meeting.

So in summary of that part, about the inspection issues, we felt there have been excellent ongoing cooperation and the meeting helped to exchange knowledge on the ongoing investigation amongst the regulators that will continue - that we will continue to collaborate on that.

In addition, at the meeting the Chinese scientists noted that China has instituted testing of [heparin] API prior to export. API's testing positive for OSCS contaminant will not be given a certificate of analysis and will not be exported from China and that is what we were assured by our Chinese colleagues.

Now to move to a different issue, as you know FDA has been conducting an investigation into the biological link between the OSCS contaminant and the observed adverse reaction.

We have very recently evaluated data that we feel provides a very solid mechanistic link between the adverse reactions observed after bolus dosing and the OSCS.

We plan to publish these data very expeditiously so they may be evaluated by the scientific community. It's very important we all be confident that we understand the link to ensure that the testing that FDA and others have put into place will prevent further adverse reaction.

We are aware that our Chinese colleagues are skeptical that such a link has been established. Therefore we are hoping to have further scientific dialogue with them within the next few weeks to present the data as we work together with them to resolve this complex situation.

Finally, our website contains updated information on heparin adverse events, I stress that as you know the occurrence of an adverse event in a patient taking a drug does not mean that the drug caused the problem.

With the heparin situation, the pattern of reports is the most powerful indicator. What caught our attention in heparin was the rapid increase in the number of deaths reported after heparin administration.

We now know there was an increase in November 2007 that persisted through February 2008 and returned to baseline in March and this coincided with our identification of the problem and the recalls.

That concludes our update, and I'll turn it back to Karen for questions.

Karen Riley: Thank you. There are a couple of other things I'd like to point out. Number one, we do have a new warning letter, Changzhou SPL warning letter and we can provide the links to all reporters who would like that link.

And secondly in addition to posting a fresh adverse event data we also have posted a map on the heparin website that illustrates you know where heparin,

contaminated heparin has been found in the world, the ten countries where this has been identified.

Okay, before we go to the phones for question and answers, again let me remind you that this call is for credentialed media only. We have a very crowded phone line so we can only take one question and one follow up question from each reporter.

And we do have some experts standing by to answer questions, should technical experts in case we need to call on them. So with that let's go to the phones for questions.

Coordinator: If you would like to ask a question, please press star 1. Please identify your affiliation when asking you question. To withdraw your question, please press star 2.

Once again, if you would like to ask a question please press star 1. The first question is from Peggy Peck, your line is open.

Peggy Peck: Yes, hello, thank you for taking our questions. My first question is this - I just would like to clarify what you're saying about establishing this link. Are you saying - if I'm understanding you correctly, you are confirming that it is the contaminant that caused these adverse events?

Janet Woodcock: What we're saying, this is Janet Woodcock we have data in vitro, in a test tube in other words, as well as animal data that shows that this contaminant can trigger events that would lead to these type of reactions, that's right.

That doesn't tell us everything of the whole story, but it establishes a link. And we hope to publish these data very rapidly.

Peggy Peck: Okay, and on follow - my follow up question is that do you have any additional data on these comments made by the commissioner in his testimony last week about the motivation behind the contamination of the heparin?

Janet Woodcock: No.

Karen Riley: Okay, we'll go to the next question then.

Coordinator: The next question is from Justin Blum, your line is open.

Justin Blum: Hi, thanks for taking my question, I have a question and a follow up, first you posted on the website a map showing eleven countries where heparin contamination is present.

You said there were ten countries and below the map it says ten countries have reported the presence, but which country shouldn't be highlighted in the map or should it really be eleven countries?

Janet Woodcock: We probably weren't counting the US.

Justin Blum: Okay. And the follow up question is that the Chinese are arguing that over oversulfated chondroitin sulfate couldn't be the cause of the deaths because it's been found in other countries where it hasn't lead to deaths and adverse reactions.

So they say there must be something unique about Baxter's product if it's lead to deaths and adverse reactions while these other company's products haven't.

Can you explain why you disagree with that assessment?

Janet Woodcock: Well we have seen a significant cluster of similar events in Germany as you know in dialysis patients number one. But the root of administration and the bolus administration may be related to why we saw the adverse events we did.

Certainly even in the US the adverse events did not occur in every individual who was exposed to this. So there's some biologic variation.

But we discussed this with the international regulators and it does appear that the root of administration and perhaps the amount that's administered and how fast it's administered may play a role.

Justin Blum: And if I could on this map as I look at it again where you list the countries at the bottom, the supposed ten countries, the United States is not included on the list.

The map has Japan highlighted but Japan is not included at the list at the bottom of countries. So are you saying that there was contaminated API found in Japan or no?

Karen Riley: Justin, no lies, we will circle back and fix the chart.

We'll check our fingers. We have - I just checked, there are definitely eleven countries, we left out the United States because we didn't identify the United States on the map since most people would know that that was the United States.

So we will fix that, there were eleven countries and all the other countries that are on that list were contaminated.

And you are by the way with Bloomberg News. Please identify your organization when you ask your question. Next question please.

Coordinator: The next question is from Elizabeth Weise, your line is open.

Elizabeth Weise: Hi, thanks for taking my call, Elizabeth Weise with USA Today. I'm wondering if you can run over the mechanism whereby you believe that this contaminant is actually causing this allergic reaction.

Janet Woodcock: We - it would be getting too deep into the technical weave, okay, to go over in detail, that's why we published it.

However, we think just a mediator reaction that the oversulfated chondroitin sulfate when it's rapidly injected in the blood, triggers mediators that can cause this reaction.

Elizabeth Weise: So that's why it's got to be a larger bolus to actually have this effect.

Janet Woodcock: Well our data indicates that there is a dose response on there. It's not what you think of as classically as allergy.

Elizabeth Weise: Okay.

Karen Riley: Okay, thank you, next question please.

Coordinator: The next question is from Bruce Jepsen, your line is open.

Bruce Jepsen: Thanks for taking my call, Bruce Jepsen with the Chicago Tribune. I wanted to follow up just sort of a broad question.

So relative to whether you have a root cause and you've established the - you know whether the causality, the intention, you know what people's intentions were in putting this in there and also is this an animal-like substance?

You said that the sulfate, it's the same thing that was found everywhere, and then you also mentioned like these ten Chinese companies, I'm a little confused here.

Because if you're saying it's the same thing found in you know all around the world, what was it? I mean what was it and how did it get in there and what are the ten companies and were they all Chinese? I'm a little confused.

Janet Woodcock: Yes, there - to answer your last question, these are ten different Chinese companies that have been shipping API or involved in heparin manufacture where we've been able to trace back at least one lot of contaminated heparin as originating there.

Karen Riley: Does Deb Autor want to get on the call on this?

Janet Woodcock: So yeah, I'll let Deb answer, let me just finish answering the first part of your question. What we're saying, we got all the analysts around the world together who have been running these tests, okay.

And we were able to determine by all of them sharing their message and you know tests and everything that they're finding the same compound. And this compound is as we said earlier, we believe it is artificial.

In other words, it is a modified naturally occurring product that has been chemically modified. And in its modified form it mimics the biological activity of heparin.

Bruce Jepsen: But for the you know little old lady in Wilmette Illinois who doesn't know what the heck chondroitin sulfate is, I mean you had said before that this comes from like you know cow bones or something, I don't know, you know what I'm saying?

You're saying it's all the same which are around the world. So break it down for me please.

Janet Woodcock: Okay, all right.

Bruce Jepsen: And also on these ten different Chinese companies, I mean are these like big pharmaceutical companies, are they - what are they?

Janet Woodcock: All right, okay. For the - basically what we're saying is that there was something in heparin that there shouldn't have been, right?

And it's - and when we tested around the world we found that different lots of heparin all over the world have this in it and it's the same compound. Yes, it is something that could be made from animal sources and then chemically modified, all right?

So that's the first part, you'll have to be in charge of the little lady in Peoria.

Bruce Jepsen: Well ma'am,. Nobody in Peoria reads us any more.

Janet Woodcock: Okay, I'm sorry to hear that.

Bruce Jepsen: I'm kidding, I'm kidding.

Janet Woodcock: And then what was your second question?

Bruce Jepsen: About the ten - describe for me the companies, I mean are these like the Chinese version of you know big companies, are they warehouses, are they…

Janet Woodcock: Deb Autor who's the head of compliance in the Center for Drugs will describe that for you.

Deborah Autor: Yeah, there are - we've actually said at least ten, so there's actually a total of twelve Chinese companies in the supply chain for the contaminated heparin and they are located in various locations throughout China.

And they've supplied either crude heparin or heparin API. I don't have in front of me data on the size of them, I would think it's fair to say they're not all large companies.

Bruce Jepsen: What do you mean by how large, and I don't mean to dominate this but I'm hoping people will weigh in.

Deborah Autor: Yeah, I don't have that information exactly in front of me, I think that there are…

Bruce Jepsen: Five employees, a shack on a farm, or…

Deborah Autor: I don't have those data.

Janet Woodcock: Right, to be clear though, they're not making the final dosage form, they're not making the vial or whatever that ends up in the hospital.

They're supplying the heparin material that's been shipped elsewhere around the world to be made into a final form of some kind.

Deborah Autor: I probably used the term API which is the active pharmaceutical ingredient.

Karen Riley: Okay, are you all clear? Next question please.

Coordinator: The next question is from Gardiner Harris, your line is open.

Gardiner Harris: Thanks for taking my call, it's Gardiner Harris with the New York Times. I guess just to follow up with Bruce and the other question, is there some sense that each one of these ten companies was doing something that then got this contaminant in there?

Or are some of these ten or twelve companies then simply a little bit further down the stream?

Do you know - and one other sort of question and that is in discussions with Chinese officials, they - I asked them about whether they are going to allow FDA to open three offices in China as Dr. (unintelligible) said and they have said, 'Well we're in discussion about whether that offer is reciprocal and whether we need to open office in the United States.'

Can you tell me the state of your cooperation with FDA and China, you all have said previously that it's very good and improving, these sort of latest test methods would suggest to me that things are not so great.

Janet Woodcock: Are international affairs on the phone? Do we have someone from international affairs?

Deborah Autor: Let me answer the first part while you're working on that which is that we do not know at what point in the supply chain the contaminant may have been introduced, so we are not saying that necessarily each of these twelve companies introduce a contaminant to the product.

We simply said that there are twelve different Chinese companies in the supply chain for contaminated heparin.

And I think Dr. Woodcock talked about the fact that we are hoping to have further discussions, scientific discussions with the Chinese within a couple of weeks.

We understand that they want to learn more about our thinking on the scientific issues. They were able to come to the international meeting and work with us through that meeting to talk about a lot of the issues presented.

And they are also - we understand taking extra measures in China to regulate heparin and to make sure that heparin API, excuse me, active pharmaceutical ingredient is screened for potential contamination before it leaves China.

So I think there are a lot of positive signs on the horizon.

Gardiner Harris: Thanks.

Karen Riley: Great, thank you, next question.

Coordinator: Your next question is from Susan Heavey, your line is open.

Susan Heavey: Hi, in addition to the map that was put on line there's also a new table with new numbers on the deaths and allergic reaction. Before the FDA had said that they had 62 deaths that were linked to these reactions.

Is that new number now 81?

Karen Riley: That's correct.

Janet Woodcock: Yes, the - we aren't saying they're linked, we're simply saying as you know that the pattern shows that there was an increase during those months which has now gone down to baseline.

But as we have repeatedly pointed out, just because somebody got heparin and they had a reaction, it doesn't imply a causal relationship and there's always been some background incidents in these reactions reported.

Susan Heavey: And can you tell me how many of those 81 are linked to Baxter's products?

Janet Woodcock: No, these keep coming in so we have to go through a lot of them - often do not have the manufacturer's number. So at some point we will post more information on that when we're sure.

But it's that we have to follow up on all of that.

Karen Riley: Susan, I would remind you that also if you look at the month by month tally that the trend continues, that it really started in about November and it ended in about February.

Susan Heavey: Okay, thanks.

Karen Riley: Next question please.

Coordinator: The next question is from Ricardo Zaldivar, your line is open.

Ricardo Alonso-Zaldivar: Yeah, Ricardo Alonso-Zaldivar with the LA Times, thanks for taking my question.

I just wanted to ask you, other than Germany, have any other countries reported adverse reactions to the heparin? Is it only a problem with Germany and the United States?

Janet Woodcock: Yes, we have talked to all the other regulators, they have not seen increases in adverse events.

Ricardo Alonso-Zaldivar: Okay, and to follow up then, what would explain that? Doesn't that seem to strengthen the argument of the Chinese regulators that there must be something else other than this contaminant?

Janet Woodcock: Well as I pointed out, there are many people in the United States who got this who did not get an adverse event to it. And we did speak to for example some people in Europe do not use bolus dosing of heparin very often.

So we are not able to rule out the fact that there, that there could be the other problems leading to these adverse events but the fact that we've now established a mechanism by which we think this contaminant could cause these adverse events, we think strengthens the association considerably.

Ricardo Alonso-Zaldivar: Okay, and follow up on that just a second, could you explain a little bit more about the mediator reaction that you mentioned earlier?

Janet Woodcock: Sure, what we're talking about here is that looking at in the test tube if you use contaminated heparin or synthetic material, this OSCS, you can see changes in what are called blood mediators that could lead to this reaction.

In addition, these have been observed in animals. And we have emerging data, we just heard about today from another source, another group of experimenters who have also observed this.

So we think this story is starting to come together.

Karen Riley: Thank you, next question please.

Coordinator: The next question is from Alicia Mundy, your line is open.

Alicia Mundy: Hi, it's Alicia Mundy from the Wall Street Journal and thank you for taking my question.

I had just a question about the different ways that the Chinese and the United States FDA and pharmaceutical testing labs are screening for the contaminant.

Is - are the Chinese using the same kind of detection methods we are and if not are those detection methods and screening tests available to them?

Janet Woodcock: I'm not - we're not sure exactly everything that the Chinese are using or what they have available, but I think we're putting measures in place in multiple parts of the supply chain.

So the Chinese will be testing before the heparin leaves their country, but our manufacturers will be testing before they would put an API into a finished dosage form.

So there's going to be multiple steps of testing instituted. Dr. Moheb Nasr may wish to comment on this more extensively.

Moheb Nasr: Yes, this is Moheb Nasr. An analytical method [capillary electrophoresist] that was put in place, and we published last month has been used by all the regulatorial authorities around the world.

And they have concern that the value and they were able to identify the same contaminant oversulfated chondroitin sulfate. Our Chinese colleagues in addition to (unintelligible) methods have used additional methods, namely optical rotation method.

And that method is less sensitive and selective than the method that basically the other regulatory authorities are using.

Alicia Mundy: I'm sorry, so you said that method is less intensive?

Janet Woodcock: Less sensitive he said and selective. This is Janet Woodcock. However I would stress that there's going to be multiple levels of testing and the manufacturer - the USP and the European pharmacopeias are going to be incorporating the NMR method into their set of tests that would be required for heparin.

Karen Riley: So that NMR method is one of the two tests that we posted on our website to screen for contaminant and heparin API.

Moheb Nasr: That's correct.

Karen Riley: Anything further Alicia?

Alicia Mundy: No, thank you very much.

Karen Riley: Okay, thank you, next question please.

Coordinator: Next question is from Anna Edney, your line is open.

Karen Riley: Please identify yourself?

Anna Edney: Hi, I'm with Congress Daily. I just wanted to make sure that I was clear on the testing, if USP is going to be incorporating it, is it - it's going to go on indefinitely then, this isn't a you know month or year long testing.

Janet Woodcock: Yes. What we talked about at the regulator's meeting, the analysts and I know this may be in too much detail for some of the non-scientists, but that we need - not only do we need tests that would be ongoing for the oversulfated chondroitin sulfate, but we really want to have tests that really identify the heparin and are able to assess its purity.

That would be a very modern test, so there's a commitment around the world to institute those tests as the testing requirements for heparin.

Anna Edney: Okay, and if I can follow up, the byproduct that you mentioned that was in excess amounts in some of the heparin, in - it's just in large amounts can it be harmful at all?

Janet Woodcock: Dermatan sulfate is as usually is - can be a contaminant in heparin and it's been observed in other drug products. So we don't have results of it being harmful that we know of, however I would say it should not be present in

large amounts, it's an impurity and it should be controlled, you know kept to a small level.

So we will be instituting requirements I think for that as well.

Anna: Thank you.

Karen Riley: Thank you, next question please.

Coordinator: The next question is from Dawn Heefner, your line is open.

Dawn Heefner: Hi, thank you for taking the call, I'm Dawn Heefner, I'm with ABC in Philadelphia. My question concerns the Baxter plant. You had early on in the investigation asked or mentioned that you had inspected the plant.

Have you gone back to the Baxter plant, have you inspected any of the other plants that have also recalled their heparin? Thank you.

Janet Woodcock: I will have Deb Autor answer that question.

Deborah Autor: Yeah, we've conducted a series of inspections both in this country and in China to investigate this issue.

Dawn Heefner: Have you gone back since the initial - my follow up is have you gone back since the initial inspection, since the Chinese are now saying well gee maybe it happened here.

Deborah Autor: I will have to check unless (Joe), are you there, do you have that fact at your fingertips? He may not be on the call as a speaker. I don't think we have based

on what we understand so far I don't believe that that would send us back to Baxter at this time.

I'll look through my notes and see if I have that information and if I do I'll join back…

Janet Woodcock: Yeah, this is Janet Woodcock too, I would like to say to people, I know that people are focusing on inspection, but you know we got samples of this heparin and gave it to multiple analysts.

And even in their own laboratories, with all their analytical equipment it took them a while to find out there was anything different or wrong with these heparin samples.

So there are limitations to what inspections can tell you.

Deborah Autor: Right, and we found with respect to the Baxter product we found contamination in the active pharmaceutical ingredient that was used to supply Baxter.

So that would give us reason to think the contamination occurred before it got to Baxter.

Dawn Heefner: Okay, thank you. That answers a lot, thank you.

Karen Riley: Okay thank you, next question please.

Coordinator: Next question is from Kevin Freking, you line is open.

Kevin Freking: Hi, Kevin Freking, Associated Press. Chinese officials said this morning that there were allergic reactions in patients taking heparin that didn't have this contaminant in it, and can you say to what extent that is true?

Janet Woodcock: We had a discussion with the Chinese officials about this lot. We have tested this lot that they're referring to and have found contamination. They have a different sample and in their testing they did not find contamination.

But we are fairly certain because of multiple laboratories here doing the testing that this lot contains contaminants.

Kevin Freking: Thank you.

Karen Riley: Thank you, next question please.

Coordinator: The next question is from Miriam Falco, your line is open.

Miriam: Hi, thanks for taking the questions. I'm still a little confused about what the Chinese are claiming today and looking at the map with the eleven countries, and by the way you didn't list Japan, you do list the US in your list of countries under the map so I think that's where the discrepancy came from.

Who supplied the heparin, what manufacturer or distributor supplied the heparin to all these other countries? Because if it's not Baxter then that sort of would explain to me at least that it couldn't just have been in New Jersey.

And what's the next step in you investigation now and what's the advice you're giving patients who are hearing this and might be quite confused by this news?

Janet Woodcock: Okay, well let's start from the patient, okay. For the patients, our message is number one that heparin supply in the US is tested and is free of this contaminant.

Number two, we now feel we have a mechanistic link, so we feel that the testing requirements that we've put in place will prevent the occurrence of this event as far as the spike of events.

Okay, number three you're asking where did all this contaminated heparin around the world come from Baxter, no. It came - it - there was a variety of different firms that produced the heparin product in these different countries.

But what we're saying is that they were traced back to these different suppliers in China, okay. So at one point what we found out about heparin, talking to the worldwide regulators, is it's shipped all over the place.

And you know maybe it's made into a final dosage form in one country and then shipped to another country and so forth.

But when we ship - we look back at where the lots came from, they came from China, okay. Now I think - I believe what the Chinese authorities are saying though is something different, which is they are acknowledging there is a contaminant that originated in China, that's what we understand from them.

However they think that isn't linked to the adverse events that were observed in the US and Germany.

Karen Riley: Miriam is that good?

Miriam Falco: Yeah, that helps, thank you.

Karen Riley: And by the way that was Miriam Falco, CNN News.

Miriam Falco: Oh I'm sorry.

Karen Riley: Yes that was - next question please.

Coordinator: The next question is from Marc Kaufman your line is open.

Mark Kaufman: Thank you very much. Two questions, one has to do with - you were saying that now you believe that the contamination went back as far as 2006, if you could just walk us through a little bit how you came to that conclusion.

And the second question is this, the Chinese today made it clear that they did not believe that the problem was caused in China. From your perspective, you know on a one to ten scale or whatever, how confident are you that this is something that did occur in China?

And I guess a third question if I could slip it in is if this was done intentionally in the United States would that be a criminal act?

Janet Woodcock: I'll leave that last question for Deb Autor but to answer - we - first of all, let's all be clear, heparin should not be contaminated, all right?

Regardless of whether or not that contamination caused acute adverse events, it should not be contaminated. So that we have all agreed emanated from these plants that we've already talked about, okay?

Now we are fairly confident based on the biological information that we just very recently have, that this contaminant is capable of triggering these types of reactions, okay.

And it appears to be dose related, so it's quite likely some people would (seek) those that wouldn't get it and quite likely depending on the root of administration and the feed and the dose and everything, you know not everyone would get this reaction.

Deb, maybe you want to talk about the…

Marc Kaufman: But also the question of how confident are you that this - that the contamination occurred in China as opposed to somewhere else further down the line?

Janet Woodcock: There's no real dispute amongst anywhere about where the contamination originated, I don't think.

Marc Kaufman: Well the Chinese dispute it.

Janet Woodcock: No, they dispute that the contaminant caused the adverse events.

Marc Kaufman: Of the - okay, this morning they disputed that it had occurred in China too, but okay, never mind.

Janet Woodcock: I don't know, we had a discussion with China, the Chinese regulators at the meeting on Thursday and Friday and they have done testing and they have instituted testing in their country to prevent lots from being exported that are contaminated.

Deborah Autor: And they also said that they found their own heparin to be contaminated.

Janet Woodcock: They did.

Deborah Autor: So - and if you look at this point in time we don't know exactly where in the supply chain the contamination occurred, but if you look at the supply chain of all the contaminated products found around the world, the one thing they have in common is China.

Marc Kaufman: Okay. And how about that question I just - if this occurred in the United States and it was intentional, if they'd be adding the chondroitin, would that be a criminal act?

Deborah Autor: That would be a criminal act but again we don't have any reason to think that's what happened.

Marc Kaufman: Okay. Thank you.

Karen Riley: Okay, thank you next question please.

Coordinator: The next question is from Jon Rockoff, your line is open.

Jon Rockoff: Hi, Jon Rockoff, Baltimore Sun. Can you just talk a little bit more - I'm just thickheaded about the mechanism by which the contaminant causes these blood reactions that are the side effects that we're talking about.

Janet Woodcock: Right. This is Janet Woodcock. Well you know there are many ways that you can develop reactions as you know after you're administrated something or say you get a bee sting or you're allergic to something, right.

And you can get hypotension and we don't think it's that type of reaction, we think that - which is allergic we think this is something when where oversulfated chondroitin sulfate is injected into the blood, it causes things called mediators to be triggered.

And they can cause a wide range of things such as low blood pressure and we have observed that, and that's the scientific data we're talking about. We will publish this and I imagine other scientists will publish the other emerging data I referred to, and that will be clearer.

Obviously this data needs to be peer reviewed and it needs to be then viewed by the scientific community.

Jon Rockoff: I mean is this sort of mechanism present in other sorts of reactions like similar…

Janet Woodcock: Yes, yes.

Jon Rockoff: Like what would be sort of like an analogy.

Janet Woodcock: Well I suppose, you know they are different mechanisms, I can't get into it on the phone, but for example you know that sometimes you get contrast mediums to have your - to look at your kidney function.

And some people they get that and then they collapse, as an internist I've been called to resuscitate people like that numerous times. And you know the contrast medium that's injected into them suddenly causes them to develop low blood pressure.

Joh Rockoff: Thanks.

Janet Woodcock: Does that make sense?

Jon Rockoff: Yeah, thanks.

Karen Riley: Okay, we have time for one more call.

Coordinator: The next question is from Jyllian Kemsley, your line is open.

Jyllian Kemsley: Hi, I'm with Chemical and Engineering news. The mediators in the blood that seem to - that you believe are involved in this reaction, what is their normal role physiologically?

Janet Woodcock: I'm not sure we know. We - that's probably a little bit beyond my - beyond I think what we can talk about on this call.

But most of these - all these mediators are involved of course in the body's defense against one thing or another.

Jyllian Kemsley: So it's part of an immune response if not necessarily part of an allergic response?

Janet Woodcock: Well immune and allergic are very similar. This is not the classic immune or allergic response, in fact. But we believe many of these other responses of the body has, also, or, to, you know, maintain homeostasis in one way or another.

Karen Riley: Okay, well thank you all for participating in today's media call on FDA's ongoing heparin investigation.

We had two other technical experts who spoke today, it was Deborah Autor, D E B O R A H A U T O R. She's Director of the Office of Compliance in CDER and Moheb Nasr, M O H E B N A S R, Director of the Office of New Drug Quality Assessment in CDER

And also I want to assure everyone that the map has now been corrected. My ability to count beyond ten has been fixed.

And please I want to remind everyone that at the end of this call a replay will be available starting at - in a couple of hours, I guess 5:30 for a couple of weeks.

And if you have any additional questions please call me, Karen Riley at 301-827-6244 or even better, email me at karen.riley - R I L E Y @fda.hhs.gov.

Thank you and have a good day.

END