FDA MEDIA BRIEFING ON HEPARIN
Moderator: Karen Riley
February 28, 2008
4:30 p.m. EST

Coordinator: Welcome. I would like to thank you all for holding and inform you that you are in a listen-only during today's conference until the question and answer session.

This call is also being recorded. And if you have any objections, you may disconnect at this time.

Now I'd like to turn the call over to Karen Riley. Ma'am you may begin.

Karen Riley: Good afternoon. I'm Karen Riley in FDA's press office. Welcome to today's media teleconference.

We are here to provide you with an update on FDA's ongoing investigation into adverse events associated with Baxter Healthcare Corporation's blood-thinning drug known as Heparin.

Our discussion will include information about our updated public health advisory and the latest news from our ongoing inspection in China, the location of the manufacturing facility where the drug's active ingredient is made.

Here to discuss what's been happening are Dr. Sandra Kweder, Deputy Director of the Office of New Drugs in FDA's Center for Drug Evaluation and Research and Michael Rogers, Director of the Division of Field Investigations in the Office of Regulatory Affairs at FDA.

Before we get started let me set your expectations. We have not yet arrived at the root cause of these adverse events. And with that, Dr. Kweder will begin.

Sandra Kweder: Good afternoon. Thank you Karen. Today FDA has issued a new public health advisory that's in response to Baxter Healthcare Corporation's expanded recall of Heparin sodium products.

You will recall that on February 11 Baxter Healthcare Corporation stopped manufacturing all of their multi dose vials of the blood-thinning drug Heparin because of reports of serious adverse events associated with use of the drug.

The reports were serious allergic type reactions including cases that had severe hypotension or low blood pressure and possible death.

The reports were almost all in patients who had received what's called the large bolus dose of Heparin. That is a high dose delivered very quickly into the blood stream.

Since that time - since - at the time, Baxter supplied half of the Heparin used for - in those clinical settings in the United States, no recall was issued.

We concluded with Baxter that a recall calling the drug back to the company would have resulted in an immediate and severe shortage of this medically necessary drug.

Therefore it was in the interest of the public health to allow the Heparin vials to remain on the market but to be used with caution, which we advised in the Public Health Advisory.

Since February 11, FDA's Drug Shortage team has been working closely with

APP, the other Heparin supplier to determine their manufacturing capacity.

Today we can report that APP is now able to adequately supply the US market. Consequently Baxter can now take the step and is voluntarily recalling all of its multiple dose vials of Heparin and single-dose vials.

As a further precaution, Baxter is also recalling another product. And that product is called HepLock. It's a Heparin Flush product.

What that is is a very dilute solution of Heparin. It's used in small - very small amounts - to prevent blood clots from forming in intravenous medication lines.

The Heparin used in Baxter's HepLock has the same active pharmaceutical ingredient source as that what was used in the vial products that they're recalling.

Again, this is a precautionary action. There have been no adverse events reported in patients using HepLock product.

FDA believes that Baxter's decision to voluntary remove all of these product lines from the market is in the interest of patient safety and public health.

The only Baxter Heparin containing product that will remain on the market are what are pre-mixed bags of intravenous solution that are contain 500 and 1000 ccs per bag.

No adverse events have been reported with that product line. And the drug uses a different Heparin source manufacturer than does the Heparin - then do the Heparin products that Baxter's recalling today.

I want to emphasize that we at FDA understand how unsettling this whole situation with Heparin is, how unsettling and anxiety provoking the adverse event reports have been and are for healthcare professionals and patients.

So far, an underlying cause of the adverse event is not known. And it remains under investigation.

We are doing everything possible. We are determined to get to the root cause of these adverse events.

We are working with every resource that we have in FDA in the field and at headquarters.

We are collaborating with the CDC and with other government agencies and with experts around the country to get to the root cause of this problem so that the medical community can go back to treating patients and providing safe and effective care.

Karen Riley: Thank you Dr. Kweder. We'll now hear from Michael Rogers.

Michael Rogers: Thank you. In addition to providing an update about the recall, I would also like to provide an update on the status of the investigation.

After learning about the recent spike in adverse events associated with Baxter's Heparin products, FDA launched a far-ranging investigation in both the United States and abroad.

This included sending a team to China to conduct a comprehensive inspection of the Chanzhou SPL facility which makes the active pharmaceutical

ingredient for this drug.

As part of that inspection, the inspection team was asked to look at issues that may have caused or contributed to the adverse events and to evaluate whether the manufacturer was following current good manufacturing practices when making the active ingredient.

Today we can announce that our inspection team has completed their inspection of the facility.

The inspection revealed that the facility is currently not manufacturing at this time and identified a number of potentially objectionable conditions related to the firm's manufacturing process.

It's important to note that at this time we still have not identified a root cause for these adverse events. And we're still evaluating this inspectional work product and working to determine the level of significance associated with these observations.

The teams' inspection observations were recorded on what we call a Form 483 or a list of inspectional observations, which is a report of potential deficiencies.

This document is presented to the company once an in plant inspection is complete and when objectionable conditions are observed.

We will be posting a redacted version of this form on the FDA Web site shortly.

The teams' inspectional observations related to deficiencies in the plant's

evaluation of the steps it takes to remove impurities; its investigation of out of specification results; issues related to waste material flow; and deficiencies related to equipment.

It's important to note that while we're concerned about what we have observed, we aren't at a point where we can determine any links between the observations and the adverse events seen in association with Baxter's drug products.

We view a 483 as just one step in the inspection process. The complete inspectional work product includes the inspection report, the exhibits, the evidence and sample analysis results. And it is this entire package that the agency uses as well as any of the firm's promised corrective actions to make a final decision about the compliance status of a facility. This process is underway.

Our team remains in China and is continuing their investigation at other facilities that have a relationship to the API manufacturer.

This continues to be an ongoing investigation and one of the agency's top priorities. And we're dedicating all appropriate resources to this investigation.

In our comprehensive and ongoing investigations, subsequent actions may include further investigation of involved facilities, sample analysis by the FDA and involved companies and a complete study of the adverse events and any other information that becomes available.

Upon completion of the investigation, FDA will undertake any appropriate regulatory action.

Karen Riley: Thank you Michael. He mentioned the redacted 483. When that is available, you can find it by going to our home page and clicking on Heparin which can be found under Hot Topics.

We're now going to go to the question and answer phase of this teleconference. Let me remind you that this is for credentialed media only.

We have two other experts standing by to answer questions should issues in their area come up.

They are Dr. Murray Lumpkin, Deputy Commissioner for International and Special Programs at FDA and Deborah Autor, Director of the Office of Compliance at FDA's Center for Drug Evaluation and Research.

As I said, this is for credentialed media only. We're going to ask you to identify yourself and your media organization when you ask a question. And please confine yourself to one question and one follow-up question only.

So conference coordinator, let's begin.

Coordinator: Thank you ma'am. At this time, if you'd like to ask a question, please press star 1 on your touch-tone phone.

You will be prompted by our automated service to state your name to help with pronunciation.

Again, to ask a question, it's star 1. To withdraw your question, it's star 2. One moment for our first question please.

First question comes from Miriam Falco. Your line is open. State your

affiliation please.

Miriam Falco: Hi. I'm with CNN Medical News. Thanks for taking these questions. Dr. Kweder -- and I hope I said that right -- have there been any adverse event reports since February 11th since you didn't or Baxter didn't take their products off the market as you said because it would have been a severe shortage that wouldn't have been helpful to the patient?

And then Mr. Rogers, if you could tell me -- I know hindsight is 20/20 -- but the question that is begged in this situation is if the FDA would have inspected this plant in the first place, would these deficiencies in the plant have been detected and then this product never would have made it to the United States?

Sandra Kweder: I'll go first. This is Sandy Kweder. Thank you for that question.

If you remember, one of the things that we did with our public health advisory on February 11 was we and also the Centers for Disease Control specifically asked healthcare professionals and facilities to please, please report cases that they knew of or were aware of with serious adverse events in patients who had received Heparin.

That kind of request is always met successfully and people do report to us and we rely on that kind of reporting.

All total from all sources we have today 448 reports of adverse events associated with Heparin products.

I can't tell you for sure that there's not some duplication in those reports.

We are working diligently to look at them much more carefully. I would say

what I know is that if we take a look at the types of cases that are particularly of interest related to the type of events that were reported and are of concern, I think the 448 goes down to 215 reports with events of interest.

We are looking at reports that have come in to us and for events that have occurred since the 15th of December.

So yes, we've gotten more. We're continuing to evaluate those reports. It's like trying to put together the pieces of a puzzle, find commonalities among them.

In many cases we have to go back to the reporter and get more information to try and understand what happened to the patient.

Just because there's a report in a patient that took Heparin doesn't necessarily mean that Heparin caused the event. And there are all kinds of events that occur. A lot of these patients are very, very sick.

Karen Riley: Thank you. I think you asked two questions. The second question is for - Deborah Autor is going to answer you.

Deborah Autor: Yes, the second question as I understood it was had FDA done a pre-approval inspection in 2004 would the agency have found these issues and been able to prevent this episode?

The answer to that is first of all to reiterate that we do not at this point know that the problem with the Heparin is linked to the API supplier.

Second of all, this API supplier came online as we understand in 2004 and began to find API for Baxter Heparin in 2004 whereas the issue we're dealing

with now didn't manifest until late 2007.

So in fact, as we understand it, the supplier was supplying Heparin problem-free for a number of years.

So I think that had we done the inspection in 2004, there's no reason to think that we would have at that time found from the API supplier if there is one that's linked to the issue that we're dealing with today.

Karen Riley: Thank you. Next question.

Coordinator: Next question comes from Kim Dixon. Your line is open. State your affiliation please.

Kim Dixon: Hi. It's Kim Dixon with Reuters. Are you going back to the - I guess I'm hearing that there are sub sources of the Heparin that supplies people like SPL.

And are you investigating those? And what have you determined about, you know, where the actual pigs were slaughtered?

And given what seems to be some, you know, some problems with drug manufacturing in China, are you expanding the investigation to other suppliers there or are you just keeping it very narrow at this point?

Michael Rogers: This is Michael. Let me reiterate that. The inspection revealed that the firm is no longer manufacturing product.

And I also pointed out that the team is still investigating in China.

We recognize that there are a number of firms that are relevant upstream from the manufacturing process. And yes they are of interest and part of this investigation.

We're working with the Chinese government as well as the company to try to understand the records associated in identifying these workshops and other farms.

Yes, another part of that question?

Kim Dixon: Well given the scope of drug manufacturing and API from China, I mean are you going to broaden the investigation?

I know that your resources are limited but…

Michael Rogers: I think Deb Autor has a comment. But let's point out that FDA's regulations apply to API manufacturers. And as you start going further upstream, you're dealing with intermediates.

It's important to note that we will go where this investigation takes us. But it requires cooperation from a number of parties including the Chinese government and the related firms.

Deb, you had a comment?

Deborah Autor: No, I was going to say we do obviously perform inspections in China. But I was also going to suggest that Dr. Lumpkin might want to add some comments on our memorandum agreement or other excerpts relating to that country.

Murray Lumpkin: Yes hi Deb. Thanks. This is Murray Lumpkin. I just wanted to add in that on this investigation as Mike says, one of the things that's been very prominent has been the cooperation of the Chinese government has been (unintelligible) and the Visa's to send our people over there, helping us (unintelligible) better there.

(Unintelligible) to see here in our relationship and are working with our partner agencies in China is that the - not only the terms of the (unintelligible) agreement but the relationships that have been built under that between us and our counterpart agencies has been a very real live situation at this point in time.

And as Mike says, as we look at the totality of the companies that are playing into the manufacturer of this product at our primary site of concern, we have the cooperation of the Chinese. And we are looking as he says where this investigation takes us. Thank you.

Karen Riley: Thank you. Next question please.

Coordinator: Next question comes from Lisa Stark. Your line is open. State your affiliation please.

Lisa Stark: Hi. Lisa Stark of ABC News. Getting back to the question on the other - the sub companies -- and I know you're still trying to work that out and how many and all that -- can you give us any idea how many potential companies in China may have been part of this chain for this drug?

Michael Rogers: That's part of what we're assessing. Again, the team is still over there. We've just completed our inspection. And we referenced the redacted FDA 483 that's going to be posted.

But this is an ongoing investigation. And we're still waiting for information to come back from our inspection team to help us understand and diagram the network of firms that would be related to the starting material, the intermediates and as it went into the finished API product.

Lisa Stark: So you don't have any idea whether that's two other firms, five other firms? I mean you don't really have a good handle yet on the number right?

Michael Rogers: We have a better handle than we want to disclose at this time.

Lisa Stark: And I'm sorry, one other question for Dr. Kweder just to follow-up. You mentioned 448 adverse events. What are the number of deaths that are potentially associated with this at this time?

Sandra Kweder: We have had reports of all total among that 448, we have had - there are reports - remember, we ask for everything.

We have reports of 21 deaths. But it's really important to know that these are deaths from all causes.

Most of these events occurred before December. Twelve of them, the report tells us that it was a Baxter Heparin product that the patient received.

Nine of them, it was not stated. We don't know. But if we look at cases, deaths that we think have the same kind of clinical picture as the allergic type reactions that brought this up in the first place, it appears that there are four of those.

Lisa Stark: Thank you.

Michael Rogers: Let me add to a previous comment to give you a better picture of just this manufacturing process without disclosing actual firm names.

You're aware of the API manufacturer that was a subject of our inspection that we referenced that the FDA 483, a redacted version that we put up on FDA's Web site.

But the manufacturing process involves if you're looking upstream, what they call consolidators. These are facilities that get product and they consolidate it for a crude product that's further manufactured into USB Heparin.

We were - we have identified as part of our investigation two consolidators that are relevant and related to the APIs in the manufacturing window associated with these adverse events. And we have inspected those two consolidators.

Further upstream from those consolidators are a number of workshops and farms. And as we've said previously and as Dr. Lumpkin reiterated, we will go where the investigation takes us certainly in cooperation with the Chinese government.

But I just wanted to give you a picture of the various firms involved and the sequence of events towards manufacturing Heparin USB API in China.

Karen Riley: Thank you. Next question please.

Coordinator: Next question comes from Anna Matthews. Your line is open. State your affiliation please.

Anna Matthews: I'm with the Wall Street Journal. I just wanted to clarify one thing and then just ask for more detail on something else.

Karen Riley: Anna, could you speak up just a tad?

Anna Matthews: Sorry. I just need to clarify one thing and ask for more detail on something else.

The clarification was Dr. Kweder, the adverse events you talked about, the 400, you said they were associated with Heparin. Were they all associated with the Baxter Heparin products that are being recalled? Or are they associated with all Heparin…

Sandra Kweder: Okay. I can tell you that I said the total was 448 total.

Anna Matthews: Yes.

Sandra Kweder: Three hundred eighty-nine of those are - state Baxter as the source. The other - the rest are a mix or are a mix of other sources or unknown.

Anna Matthews: Do you - do we- then are the concerns that have been raised about the Baxter products, do they apply to these other Heparin products?

Sandra Kweder: To date most of our concern remains with the Baxter - our concern remains with the Baxter product.

We don't have reports that lead us to believe at this point in time that there are problems with any other products. But we are watching very carefully for that.

And it's one of the reasons in our public health advisory today we continue to

ask healthcare providers and institutions to please report any cases that you have.

Anna Matthews: And then I wondered if - the list of things that you said you had found -- I think this was for Mr. Rogers -- in the inspection of the Chanzhou plant, I was writing as fast as I could, but do you think you could go through those again and maybe elucidate a little bit what you mean by them and which are of most potential concern?

You've mentioned waste material flow, equipment deficiencies and steps they took to document things. Could you walk through those again and explain what they mean and which ones are most serious?

Michael Rogers: Part of your question is asking the agency to make a final determination about the significance of these observations. And I think that would be inappropriate at this time given what we said earlier in that this - the FDA 483 is just one part of the inspection work product.

It includes the EIR. It includes the exhibits, includes analytical results as well as a total evaluation of those inspectional findings as well as whatever the firm may commit to to make changes.

Having said that, the exact language of the 483 I would direct you to FDA's Web site. And we made - we announced that we would be posting a redacted version.

I don't want to get into talking about the significance of the 483. I used a term EIR. And let me clarify what that means. That is Establishment Inspection Report.

But I'd just rather not get into talking about the significance of the observations. I direct you to the FDA Web site.

Anna Matthews: Without doing that then, would you be willing to just repeat the observations that you mentioned? Because it hasn't been posted yet.

Michael Rogers: It will be shortly.

Anna Matthews: Okay.

Sandra Kweder: This is Sandy Kweder. You know, one of the things as one of the clinicians and reviewers, the way that we think about, you know, of a really basic lay person's interpretation of a 483 is that it's a list that the inspector develops while they're going through a facility, things that need to be further followed-up on as potential areas of concern.

And if you look - when you see it, when it does get posted, you'll see that it's stated as it's a preliminary or a draft. And it's - and we don't base specific conclusions on the 483 itself.

It's a working list that we use to then go back and work with the firm and ask them further questions about, ask them to explain more.

And I think that's one of the reasons that you're hearing some reluctance to say what's the most important because we really don't know what's the most important. Anything's potentially important.

Anna Matthews: Okay.

Karen Riley: Okay thank you. Next question please.

Coordinator: Next question comes from Luke Timmerman. Your line is open. State your affiliation please.

Luke Timmerman: Hi. I'm with Bloomberg News.

My question was that John Jenkins on the February 11 call said that there could be other factors here besides manufacturing to blame like maybe rubber stopper components falling off in the fill and finish phase.

I wonder if any factors like that have been ruled out so far in the investigation?

Deborah Autor: This is Deborah Autor. I think it's fair to say that we're still considering all possibilities. We have not yet identified the root cause. We have not ruled anything out at this point.

Luke Timmerman: Okay, the other follow-up was how many members are on this inspection team? And how many of them speak fluent Chinese?

Michael Rogers: We covered that at our previous media call. But the team is composed of two individuals, one of which is a national expert in drug manufacturing technology and a person that has domestic and international experience conducting complex inspections.

The other person is a PhD who speaks fluent Chinese and has in-depth knowledge and understanding of the actual application as well as the Heparin manufacturing process.

Luke Timmerman: Thank you.

Karen Riley: Thank you. Next question please.

Coordinator: Again at this time, if you'd like to ask a question, please press star 1. Our next question comes from Mark Kaufman. Your line is open. State your affiliation please.

Mark Kaufman: With the Washington Post. This is kind of to follow-up on Anna's question before. You put us at something of a disadvantage if we can't see the 483 while you're still on the phone. So we can't ask questions.

So I guess I'm going to pose this as a question. Why did you not make that available before the press conference or the teleconference so that we could ask questions about it?

And the second thing is, you know, in the absence of that, could you explain to us going back to what you had said earlier, what are the areas of concern without saying this is a cause or that is a cause?

But from your view, what were the areas of concern since we're not going to be able to answer the question after we've seen the 483?

Karen Riley: Yes we're going to read those bulleted observations since I guess it's still not there. Okay, Michael?

Michael Rogers: The team's inspectional observations relate to deficiencies and the plants evaluation of steps it takes to remove impurities; its investigation of out of specification results; and issues with waste material flow; and deficiencies related to equipment. That's the general characterization of the observation.

I'll add that a lot of the observations relate to process validation and control. We're told the 483 redacted version is up.

Karen Riley: Can you say what process validation and control is? I'm not sure they all know what that means.

Michael Rogers: The firm's demonstrated ability to manufacture the product over a consistent period of time that meets USP specifications as well as any self-imposed specification.

Deborah Autor: This is Deborah Autor. And I just want to emphasize one point which is even had the 483 been up before this call, I don't think that we'd be prepared to go through the observations in detail.

As Mike Rogers has said, those are preliminary observations. And we don't yet have our investigators back in this country. When we have them, we have their full establishment inspection report and we're able to really dig underneath here and evaluate the significance of this, I think we'll be better able to talk about it.

But at this point what we have is a preliminary set of observations which we wanted to share with you but which we're not yet ready to discuss in great depth.

Karen Riley: Thank you. Next question please.

Coordinator: Next question comes from Daniel DeNoon. Your line is open. State your affiliation please.

Daniel DeNoon: Hi. I'm Dan DeNoon with Web MD. Can - Dr. Kweder, can you give me -

give us some indication of how much Heparin this is, how many doses of the multi vial and how many doses of the single vial are being recalled?

Sandra Kweder: No, honestly I don't have those numbers in front of me. But one of the things that's important to know is that the way that Baxter produces Heparin, they don't have a very - you know, the time between its actual production and the time it reaches the facilities, there's not a lot of inventory between there. It tends to get used and then reordered very quickly.

So they stopped production early in February 10 or 11. Much of the Baxter product that people would have had available is mostly used up in - for most institutions.

And so - and they had not been able to order any more. So it's - what our understanding is that there's not a lot - as much to recall today as there would have been to recall back on the 11th of February.

And meanwhile, distributor sources have been ramped up substantially by APP.

Daniel DeNoon: Is there - just as a follow-up, is there any gap or lag time between the ability of APP to make up - to re-establish the flow of Heparin?

Sandra Kweder: APP has - you know, we have a drug shortages team that works very closely with manufacturers and to understand the whole flow.

As with any potential shortage or in any recall setting, there may be small pockets of areas where there might be a little bit more difficulty than others.

But APP has been working very hard to make sure that there aren't gaps in

supply. That's particularly the case for the Heparin in vials, you know, the multi dose and single dose vials where they are the only other manufacturer for the US.

For the HepLock and the HepFlush, I believe there are seven manufacturers that can fully supply the market immediately.

Daniel DeNoon: Thank you.

Coordinator: Next question will come from Peggy Peck. Your line is open. State your affiliation please.

Peggy Peck: Hi. This is Peggy Peck. I'm from MedPage Today. And I think that my first question was answered (unintelligible) want you find out whether or not (unintelligible) for HepLock. And you've just covered it.

Karen Riley: We can't hear you Peggy.

Peggy Peck: I'm sorry, can you hear me now?

Karen Riley: Yes.

Peggy Peck: Yes okay. I had - I believe that my - I did have a question about HepLock and whether there were other manufacturers available for that.

But in addition to that, I'm wondering, I want to get into this - the inspection teams in China whether or not you've had any discussions with the Chinese government about inspections of these workshop type facilities that we've heard described.

It appears from news reports that they have never been inspected. And I'm wondering if there has been any indication from the Chinese, from your Chinese counterparts that they would consider inspections at that level?

Michael Rogers: We're - as Dr. Lumpkin mentioned, we're exploring all of that is where this investigation may lead us with the Chinese government.

As you go further upstream from the process I described from the Heparin USP manufacturer, the API, one level upstream to the consolidators and even further upstream FDA's regulations and their criteria by which we use to assess the products coming out of those firms is - it's become difficult.

We believe that we'll continue to work with the Chinese government perhaps in a collaborative effort, work with them and try to better understand their oversight of these facilities.

But it's still as we mentioned, an ongoing investigation.

Peggy Peck: And on follow, do you have any sense of the numbers of that way upstream, those workshops that there might be?

Michael Rogers: We have records that indicate and may suggest the number of workshops that may have contributed to the two consolidators that we inspected that provided crude materials to the API manufacturer that was the subject of the original and first inspection.

We need to verify that information and we're currently doing that.

Peggy Peck: So that information has been redacted from the report. Is that correct or it's not…

Karen Riley: We've gone over time. And I want to thank you for participating and apologize for the 483 not being posted.

But we're going to get with our Web staff and get it posted ASAP. So you can be confident that that will happen.

We also want to tell you that a replay of this briefing will be available starting at 6:00 pm.

And if you have any additional questions you can contact me, Karen Riley.

Thank you very much.

Coordinator: At this time, that would conclude today's conference. You may disconnect and thank you for your attendance.

END