FDA Media Briefing on Heparin
Moderator: Karen Riley
Monday, February 18, 2008, 1 p.m. EST

Coordinator: Good afternoon and thank you 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. To ask a question at that time, please press Star 1 and record your first and last name.

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

I would now like to introduce your host for today's conference, Ms. Karen Riley with the FDA.

Karen Riley: Good afternoon and welcome to today's teleconference for credential media only. I'm Karen Riley with FDA's press office.

A week ago, the FDA warned health care providers and their patients about a spike in the number of adverse events involving the drug Heparin manufactured by Baxter Healthcare Corporation.

Baxter agreed to a temporary halt in manufacturing of multi-dose vials of the blood thinning drug until experts could find a cause of the adverse events.

Today we want to tell you about the steps we've been taking to investigate these adverse events both in the United States and in China and to flesh out for you what an investigation of this sort really entails.

Let me be very clear so you can set your expectations at the start. We are not here to announce that we've discovered the root cause of the problem nor or we here to revise our health care advisory on heparin.

We continue to advise doctors and other health care providers to seek alternative courses of heparin and if they cannot, they should be cautious when administering the Baxter product to their patients, especially a bolus administration of the drug.

With that, let's begin. With me today is Michael Rogers, Director of the Division of Field Investigations for FDA's Office of Regulatory Affairs who is spearheading much of the investigation.

Michael has an opening statement and then we'll open the phones for questions for him or for the other experts from FDA and the CDC that we've assembled here. Michael.

Michael Rogers: Thank you Karen. It's important to mention at the outset that at the present time we don't know what is causing these adverse events and that we have an ongoing investigation that involves domestic and international inspections, analytical support and close cooperation with the firms involved.

I can tell you that the agency considers this as one of its top priorities and is dedicating all appropriate resources for this investigation.

I think it's important to talk about the process that the agency typically follows when investigating adverse events associated with an unknown cause that appear to relate to a common product with the end goal being to find the root cause for the adverse events and get control of the product.

We begin at the patient's bedside and go all the way back to the raw materials used in the initial manufacturing process, methodically looking at every step. This process requires investigating patient records and will essentially validate the criteria used to define the adverse events that fall outside of what you would normally see associated with this product.

In addition, it involves talking with the firms, the medical community and working with CDC and other partners. Ultimately, the scope of an investigation like this is designed to identify the extent of the problem and the manufacturing window of the problem as well as identify the volume of the product in commerce.

As part of this process, we are also interested in learning about the raw materials that were used to make these products as well as any related firms involved in manufacturing or having received these products.

We have an ongoing inspection at Baxter's Cherry Hill, New Jersey facility and at the supplier scientific (protein) labs in Waunakee, Wisconsin. This week we'll have an inspection team on the ground in China ready to begin a comprehensive inspection of the Changzhou SPL facility which makes the active pharmaceutical ingredients for this drug.

The team includes an expert in drug manufacturing technology who has experience conducting complex inspections in the domestic and international arena. It also includes a chemist who speaks fluent Chinese and is very familiar with the heparin manufacturing process and the operations of the pharmaceutical industries in China.

Our investigators in China will have a number of tasks before them. The inspection team will be conducting a comprehensive good manufacturing

practice inspection at the Chinese facility that's designed to determine if the firm is in compliance with FDA's regulations.

We'll also be focusing on the firm's manufacturing process and how it adheres to the literature in the drug applications. They will conduct a thorough review of the history of the plant including its business relationships, supplier, customers, as well as any other products they may make.

This will cover employee training, examine how the company stores and tests raw materials, check to see what the plant's equipment that is operating properly and go through an extensive records review including lab tests, batch records and other data in search for deviations or anomalies.

None of our investigators are entering these facilities with any preconceptions. In China, as elsewhere, we intend to be there as long as it takes to rule out or rule in the facility as a root cause for these adverse events.

All good investigations take time and involve a meticulous analytical process. With this investigation, as with others before it, we will follow the evidence where it leads. It's important to reiterate that right now, in that we don't know the source of the problem and we believe it would be a mistake to speculate on what it might be.

Although root – no root cause has yet been established, let me assure you that we're taking every necessary step to find out what happened so we can avoid any future adverse events of this product.

Let me close by saying that we know how unsettling these adverse events have been for doctors and patients and it is our goal to close this out as

effectively and efficiently as possible so that the medical community can go back to treating patients and providing safe and effective care. Karen.

Karen Riley: Thank you Michael. That was Michael Rogers, Director of the Division of Field Investigations for FDA's Office of Regulatory Affairs who is spearheading much of our investigation.

We'll now go to the question and answer portion of this teleconference. And before we begin, let me remind you this is for credential media only. We're going to ask our experts when they're called on to answer a question to identify themselves prior to answering the question.

Conference coordinator, let's see who has some questions.

Coordinator: Thank you. If you would like to ask a question, please press Star 1. If you have muted your phone line, please unmute and record your first and last name. To withdraw your question, press Star 2.

The first question comes from Miriam Falco of CNN Medical News. Your line is open.

Miriam Falco: Hi, thanks for taking the question. Can you tell us exactly when you're going to be in China, how long you're going to be there, who you're going to meet with and also you told us last week that you're not required to inspect these facilities, at least not by law, but it is policy. Can you clarify that a little bit please? Why wouldn't it be something that you would want to inspect when it's the element for the drug that is manufactured by this company that's sold – drug sold here in the U.S.?

Michael Rogers: This is Michael Rogers and I'll address the first part of the question and then ask Joe Famulare from our Center for Drugs to address the other parts of your question.

We expect our inspection to begin this week. That inspection will collaborate with firm officials at Baxter as well as in China. As far as how long it's going to take, we've given this team the flexibility to extend this inspection as long as it takes as well as investigate the appropriate leads within China.

Joe Famulare: This is Joe Famulare, Deputy Director, the CEDER Office of Compliance. With regard to the latter part of your question, the facilities that supply ingredients for manufactured finished products here in the United States are inspected by policy prior to approval of an application.

And they are required to meet the current good manufacturing practice requirements and to fulfill the ability to meet the requirements in the applications to clarify that, so by policy, we will inspect those. Thank you.

Karen Riley: Thank you. Next question please. And please identify yourself.

Coordinator: The next question comes from Bruce Japsen of the Chicago Tribune.

Bruce Japsen: Thanks for taking the call. I was wondering, you've said that the production of heparin is now being done, or you've asked APP, American Pharmaceutical Partners, to ramp up its production. They also get their products from China. Has their facility been inspected? And also how many drugs are coming in to the United States from either – that have – with no inspection of facilities by either the FDA or the Chinese FDA?

Joe Famulare: In terms of this...

Karen Riley: This is Joe Famulare.

Joe Famulare: Sorry, this is Joe Famulare, CDER Office of Compliance again. With respect to the other facility, APP -- that has passed the satisfactory inspection with the FDA.

The firms that are named in applications from foreign countries are inspected before the application is approved in all instances. There is – in this isolated incidence, this has not been done beforehand. However, we are, you know, well on the way to inspecting that facility now. Thank you.

Karen Riley: Thank you. Next question please.

Coordinator: Once again, if you would like to ask a question, please press Star 1. The next question comes from David Greising of the Chicago Tribune.

David Greising: Yes, thank you. Just a follow up on that answer from Mr. Famulare, we were told by one of your colleagues of the FDA last week that in fact the – there are many drugs that come into the U.S. from China with no inspection because the Chinese authorities, the Chinese FDA does not inspect plants that manufacture for export only.

In other words, if they don't distribute it within China, the Chinese FDA does not inspect them. And since Senator Grassley from Iowa put out some data last week saying that in the last several years the number of FDA inspections in China has run somewhere between 11 and 20 inspections and certainly there are more plants then that obviously that are distributing in the U.S.

So can you please clear up that question of whether in fact, Chinese production facilities are inspected prior to distribution to the United States?

Joe Famulare: This is Joe Famulare once again. When an application is filed with the FDA, the facility that is going to produce the dosage form or in all likelihood in the case of China, the active pharmaceutical ingredient manufacturer, is named in that application. FDA will inspect it prior to approval of the application.

Now in terms of how many inspections we do there every year in China, the pre-approval inspection prior to approval of application is the priority. The numbers you cite are within the general range.

The other aspect of the question you asked, does China inspect those that are exclusive for U.S. only? In – at least in the instances we are aware of, they do not do those inspections now. So that FDA goes and does those inspections again prior to the approval of the application.

David Greising: So you're saying that most plants that send API of other pharmaceutical ingredients to the U.S., you're saying that the only one that hasn't been inspected is this particular one, this heparin one, is the only one with specific cracks so far as you know?

Joe Famulare: So far as I know, in terms of our intent to inspect all prior to approval of the application, this facility is an isolated incidence right now. Now in terms of what I'm – my – the scope of what I'm talking about, I'm talking about products for which applications are necessary.

David Greising: I mean – can you explain to us what do you mean – why is that distinction an important distinction for us to understand?

Joe Famulare: Because there are other products that may not require abbreviated new drug applications or new drug applications and those are inspected on a surveillance basis.

David Greising: Okay, thank you.

Coordinator: Once again, if you would like to ask a question, please press Star 1. The next question comes from Marc Kaufman of Washington Post.

Marc Kaufman: Thank you. I was just confused by the last comment. Are you saying that if it – if the application – I'm not sure what you were saying. If the application is coming from a new drug product application or an abbreviated drug product application, I mean, that's all the world of prescription drugs.

So you're saying that if they are in those two categories they do not have to be inspected?

Joe Famulare: No, they will be inspected as policy prior to the approval of the application.

Marc Kaufman: Okay, again our limited understanding is that we're looking at hundreds or thousands of products that, you know, whether they're DMF that are filed and then different companies say that they want to use that product.

There are hundreds of thousands every year and yet the number of inspections abroad is in the, you know, the dozens. So how could we possibly be covering all the ones that are being filed?

Joe Famulare: I don't know where you're getting your numbers of DMFs and so forth. What we base our information on are current filings of applications within FDA, the sources named within those applications.

DMFs are on file but they're not necessarily active. What is active is those that are being referenced and applications for approval. When they're referenced, we have certain timeframes when – and different disciplines that look at the applications.

One important discipline is inspection and that inspection discipline will weigh-in before the application is approved with satisfactory results or that can be delayed, the approval of the application. And just to clarify, the DMFs that you're referring to are drug master files.

Marc Kaufman: Okay.

Karen Riley: Who can explain for those who don't know what a drug master file is?

Eric Duffy: Yes, this is Eric Duffy. I'm the director of post-marketing evaluation for CMC in CDER. A drug master file is a file which describes all the manufacturing controls for an API.

This system is put in place so that a manufacturer of an API can provide to FDA all the required information even though it may be trade secrets or proprietary in nature. FDA then has the opportunity and the access to all the information that's required.

Karen Riley: Is that good Marc?

Marc Kaufman: Well, again, I'm really quite confused here because I looked at some statistics several years ago involving the number of DMFs that had been activated that had come from India and that had come from China and there were scores of them, if not more.

That was just in one year, and yet the inspection numbers don't – are not consistent with that. So I'm just trying to understand the difference.

Joe Famulare: Marc, I think you can maybe follow-up later for more detail. This is Joe Famulare again.

Marc Kaufman: Okay.

Joe Famulare: And again, you have to correlate the inspections done against applications and the fact that we not only do inspections, we also use inspection history if it's a recent inspection, so the idea is for every application we will look at those site names, be they domestic or foreign, we will clear those sites in the Office of Compliance based on recent satisfactory inspections or the need to do a new inspection.

I don't think you're going to find a correct correlation, as you say, between DMFs and inspections. I – it's not a good corollary for you to use in this instance. Thank you.

Marc Kaufman: Thank you.

Karen Riley: Thank you. Next question please.

Coordinator: Your next question comes from David Greising of the Chicago Tribune.

David Greising: Yes, thanks again. I just – and I'm sorry – I guess unless you want to have to follow up with all of us. I think there's still a little bit of confusion here. I'm getting the impression that if somebody registers a plant overseas as part of

their production process within the FDA, it kind of lights up as something that needs to be inspected by the FDA.

Is it possible that a pharmaceutical company that uses a foreign producer of an F – of an API would not notify the FDA of that source and therefore would not – it would not come up as something that needs to be inspected?

Joe Famulare: This is Joe Famulare from the CDER Office of Compliance. There are several requirements for the importation of active pharmaceutical ingredients either into the U.S. or for use by another foreign facility let's say that'll make the dosage form or bring that dosage form in the U.S.

So what you've asked is a multi-layered question. Registration is a requirement in order to produce products for – you know, either active pharmaceutical ingredients or drug products to be shipped into the U.S.

Now firms may register but may never go ahead with their business plans or may never ship, okay. There's second layer of information or process within FDA to deal with a dosage form that's going to be approved and that's what I've been talking about and that's the requirement to name the facilities within the application that you intend to produce your active pharmaceutical ingredient and your finished product.

That's primarily what we've been focusing on here. And based upon that, we will look at our inspection records for the facilities named. If we have inspectional history, that's adequate and in compliance. We'll be able to reference that facility.

Or if it's not been inspected before or there're questions about that firm's ability to perform the function or issues from previous inspections, we will do an inspection before the application is approved.

Now there's a whole host of regulations for products not subject to applications, et cetera, ways that we monitor products and active ingredients coming into our import systems as well, to trace what they are, what we know about them and they meet the requirements of the law. Those are beyond this specific situation.

David Greising: Right.

Joe Famulare: This situation with heparin coming from China active ingredient coming to a plant here was a situation where we'll identify the firm in the application and evaluate that firm, that API manufacturing facility. I hope that adds a little bit more clarity.

David Greising: Yes it does. And if I might follow-up, when we're talking about inspections, because in some of the responses to questions that we were posing last week, both to the company and city agency, it appeared that sometimes an inspection basically amounts to an approval of paperwork that is filed and not necessarily a visit to the physical premises where the pharmaceutical agent might be produced.

Just to be clear here, is an inspection, in fact, a visit to the site or might it just include – might it just be comprised of a review of paperwork?

Joe Famulare: Let me just distinguish two areas here. This is Joe Famulare again. When a facility is named in an application, it requires an evaluation of its sufficiency

to produce what it says it's going to produce in the filed application and it needs to be in compliance with current good manufacturing practices.

If we have recently inspected the facility and it's named in application, a physical inspection has been done recently, we can reference that inspection for allowing it to be referenced in another application.

If that situation is not in place, we will go and do a physical inspection to ensure that they are in compliance with GMPss at site, current good manufacturing practices, and that they can do at that site what is cited in the application, manufacture a product and do whatever processes and testing or other issues that are named there. Thank you.

Karen Riley: Thank you. I think we have time for one more question.

Coordinator: Thank you. The next question comes from Miriam Falco of CNN Medical News.

Miriam Falco: Taking a giant step backwards, and I apologize because I wasn't on the call last week, so then how does this facility for drugs manufactured by a company that makes 60% of the heparin used in this country. How has this facility not yet inspected? Had it been inspected for something previously and thus you had the situation you just described or how does this not happen?

Joe Famulare: This is Joe Famulare once again. When this site was named in the application, the firm that was selected and sent to the Office of Compliance for evaluation was not the correct firm. It was another firm with a similar name. We therefore evaluated the firm with the similar name which had an in-compliance recent inspection history. Therefore, this particular firm was not put forward for evaluation.

We have discovered that. We're acting upon that by doing our immediate inspection. We're looking at this process and we have not found any other firms in this category. And to date, this is an isolated situation but the wrong firm was put into the database, therefore this one was not evaluated or scheduled for inspection. Thank you.

Miriam Falco: Well, can I follow up though? Who did – who put the wrong information in the database and how is it that this was – was this detected after the adverse events were reported and only because somebody looked at that again? Or was this detected independently of the whole adverse event situation?

Joe Famulare: This is Joe Famulare once again. We are still in the process of studying this situation and dealing with that individual issue. And when I said we've looked at this and discovered this within the past month and we found that this was the situation, so therefore we've acted immediately to organize quickly an inspection of this firm. Thank you.

Karen Riley: Conference Coordinator, do we have anyone else left in the queue?

Coordinator: We do have one additional.

Karen Riley: Take that last one – last caller then please.

Coordinator: Thank you. The question comes from Anna Mathews from Wall Street Journal.

Anna Mathews: Hi. You mentioned that you had inspected the plant that makes heparin API for APP. I'm curious whether there are any other makers of heparin API in China and that supply that for the U.S. market that you're aware of and if they have been inspected.

Joe Famulare: To the best of my knowledge – this is Joe Famulare. Once again, there are two approved dosage form manufacturers that use the two China sources that were talked about in the call. I'm not aware of any others. Thank you.

Karen Riley: Does that help you Anna?

Anna Mathews: So there are two approved, which is APP and Baxter, and two Chinese suppliers, the two that we just discussed?

Joe Famulare: That's correct.

Anna Matthews: Thank you.

Karen Riley: Is that it?

Anna Matthews: Wait. And you've inspected – so you inspected APP and you're about to inspect the supplier for Baxter as we discussed?

Joe Famulare: The supplier for APP has been inspected and we're about to inspect the supplier for Baxter.

Anna Mathews: Okay, thank you.

Karen Riley: Okay, I guess that this then concludes our teleconference on providing you with an update of our ongoing investigation into the cause for these adverse events involving the injectable heparin manufactured by Baxter Healthcare Corporation.

Before I close, I just want to provide a message to those news organizations that have a bureau in China. We know the public is very interested in getting to the bottom of this and so is FDA.

But for those media that do have bureaus in China, we ask that you let our experts do their work there as quickly as possible. Since we're in direct communication every day with these experts, please direct your questions to us.

This then concludes our call. If you have any additional questions you can call me, Karen Riley, at 301-827-6244 or please use my email address at karen.riley@fda.hhs (as in Health and Human Services).gov. And let me remind you that this call will be available for I believe a couple of weeks and the replay number is 1-866-459-3509. Thank you.

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