Transcript of FDA Press Conference on Adverse Events Associated with Baxter Healthcare Corporation's Multiple-Dose Vials of Injectable Heparin

Moderator: Karen Riley
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Coordinator: Welcome and thank you for standing by. At this time, all participants are in a listen-only mode until the question and answer session today's conference. At that time, you may press star, 1 on your touchtone phone to ask a question. I would now also like to remind parties this call is being recorded. If you have any objections, please disconnect at this time.

I would now like to turn the call over to Miss Karen Riley. Thank you ma'am, you may begin.

Karen Riley: Thank you. I'm Karen Riley in FDA's press office. Welcome to today's media call to discuss what is being done about serious adverse events associated with Baxter Healthcare Corporation's multiple-dose vials of injectable heparin.

With me today, is Dr. John Jenkins, Director of the Office of New Drugs, at FDA's Center for Drug Evaluation and Research as well as other experts from FDA and the CDC. Dr. Jenkins will provide some opening remarks, then we'll open the phones to questions. Dr. Jenkins…

John Jenkins: Thank you Karen, and hello to everyone on the phone. Today FDA's announcing that Baxter Healthcare Corporation has temporarily halted

the manufacture of its multiple-dose vials of heparin for injection because of recent reports of serious adverse events associated with the use of this drug.

Serious allergic reactions, cases of severe hypotension or low blood pressure and four deaths have recently been reported in patients who received a large, bolus dose of the drug – by that, I mean a high dose delivered very quickly into the bloodstream. I should note that while we have received reports of four deaths, at this time it is not possible for us to establish a relationship between the deaths and the use of heparin in those cases.

Since late December, Baxter and FDA have received approximately 350 adverse event reports and approximately 40% of those reports have been characterized as serious. FDA is currently conducting a careful analysis of these reports to better understand the nature of the events and to ascertain any patterns that may help to pinpoint the root cause.

Heparin, as you may know, is an anticoagulant, or in lay terms, a blood thinner that is derived from pigs. Heparin has been widely-used in the United States since the 1930s. Heparin is used in a variety of medical settings, including for patients in kidney dialysis centers, in certain types of cardiac surgery, and in hospitals to prevent and treat blood clots such as deep vein thrombosis or DVT and pulmonary emboli. In many of its uses, heparin is life-saving or life-sustaining and it is considered to be a medically necessary product.

FDA is currently collaborating with Baxter, the Center for Disease Control and Prevention, and other internal and external experts to determine the root cause of these serious adverse events. FDA's field

investigators and scientists are conducting inspections of all facilities and processes involved in the manufacture of Baxter's heparin. FDA scientists and investigators are also conducting our own extensive tests of samples of the Baxter heparin product. To date, a cause for the reported adverse events has not been identified.

While FDA continues its comprehensive investigation, the multiple-dose vials of heparin manufactured by Baxter that are currently in distribution will not be recalled and may continue to be used with caution by physicians and other healthcare professionals. Baxter supplies approximately half of the multiple-dose vials of heparin used in the United States and a recall would result in an immediate and severe shortage of this medically necessary drug. Therefore, after careful consideration, FDA has concluded that it is better for the public health to allow the Baxter multiple-dose vials of heparin to remain in distribution so they can be used with caution in situations where use of heparin is considered medically necessary and alternate sources of heparin are not available.

The other approved manufacturer of multiple-dose vials of heparin is APP Pharmaceuticals. FDA is investigating whether a similar increase in adverse reaction reports has been seen with APP-produced heparin and other heparin products. At this time, no such signal has yet been detected.

FDA is working with APP and other manufacturers, including foreign manufacturers, to identify alternate sources of heparin to fill the void that will occur if the Baxter manufacturing suspension continues. I would note that Baxter will continue to manufacture and distribute its single-dose vials of heparin. However, healthcare providers should be aware that serious adverse events of the same type I described earlier

have been reported in a few cases where single-dose vials of Baxter heparin were combined in order to give a large bolus dose to a patient.

It appears that the adverse reactions we are seeing are related to bolus dosing and therefore, even using single-dose vials to generate the dose necessary to give the bolus could be of concern.

FDA is offering advice to healthcare providers on how they might proceed, given the current situation with the manufacturing suspension of Baxter heparin products. FDA's advice is intended to try to reduce or mitigate the chance that serious adverse reactions might occur while the investigation is continuing.

Our advice is as follows – number one, healthcare professionals should administer the drug as an intravenous infusion not a bolus dose whenever possible. Number two, healthcare professionals should use the lowest dose necessary at the slowest rate of infusion acceptable to attain the desired clinical effect. Number three, patients should be carefully monitored for adverse events and there should be adequate trained medical personnel and equipment for resuscitation readily available to intervene should a serious adverse event occur. And finally, depending upon the individual patient circumstances, physicians should consider the potential benefits and risk of pre-treatment with corticosteroids or cortisone-type medicines or antihistamines or drugs that relieve the symptoms of allergic reactions.

I would emphasize, however that at this time, FDA does not have data to say whether such pre-treatment may be effective in ameliorating or reducing the risk of an adverse reaction. And with that, I will stop and open it up for questions.

Karen Riley: Thank you, Dr. Jenkins. Now Dr. Jenkins and our other experts are available to answer your questions but before we go to the phones, let me remind everyone that this call is for credentialed media only. Okay, let's get started. Conference coordinator?

Coordinator: Thank you. We will now begin the question and answer session One moment please, while we wait for the first question.

(Gardner Harris), your line is now open.

(Gardner Harris): Hi. Thanks for doing the call. This is – I have nothing but the obvious to ask, and that is, do you all have a sense that this is a new risk that you are uncovering? Is this a risk that has sort of been there you think, that you're just now becoming aware of? Is – can you tell us anything about Baxter's manufacturing process – did they sort of recently change it? Is there something going on – this is from my editor – we recently wrote a story about people in Austin, Minnesota having a reaction at a plant to pig's brains. Is there anything going on here about sort of a reaction to the pig part of this?

John Jenkins: All right, (Gardner), let me get started with – I'll try to remember all those parts.

(Gardner Harris): I'm sorry.

John Jenkins: That's okay. The first question relates to, does this appear to be something new and the answer is, yes. There is a low background rate of adverse event reporting for heparin, including serious allergic reactions but those occur at a fairly low level. And looking back over the last several months of our AER's -- Adverse Event Reporting system data, it's clear that this spike in reports started coming in to

FDA toward the end of December and really have escalated during January. So this is a new phenomenon on top of the background of a low rate of adverse events.

As far as the manufacturing, the product is sourced from pig intestines and then goes through multiple purification steps to inactivate proteins and viruses and extract out contaminants before it reaches the final dosage form. Heparin is actually a complex mixture of carbohydrates that serve as anticoagulants. And one of the things that we are carefully looking at is whether there are any issues that have arisen during the manufacturing process, the purification process that may have resulted in either introduction of a contaminant or failure to remove protein or to inactivate protein that's normally present and accrued extract from the pig intestines.

I would point out that at this point, we really don't know the root cause of the problem and why we're focusing a lot of attention on the manufacturing of the heparin, it's also possible that the source of this problem could be things further along in the manufacturing chain, such as the vials that the heparin is packaged into, even the rubber stoppers. There have been instances in the past where changes anywhere along the manufacturing chain can result in allergic-type reactions like the ones we're seeing here.

I think I covered at least two of your questions. The pig brain issue, I think, is probably unrelated, but I'm not familiar with what the report was from Minnesota about pig brain issues.

(Gardner Harris): Thank you, doctor.

Karen Riley: Thank you. Next question – and before we take that question, let me make sure that you tell us who you work for when you're asking your question, and also, we're going to restrict you to one question and one follow-up per person. Okay, go ahead.

Coordinator: Next question comes from (Cheryl Townsend). Your line is now open.

(Cheryl Townsend): Hi. I report for American Journal of Health System Pharmacy. Would you please define high bolus dose as in number of units of heparin?

John Jenkins: Yes. Again, this is John Jenkins. We've seen reports associated with doses as few as several thousand units and in some patients they have received doses as high as 40-50 thousand units but it really does seem to be associated with the bolus dosing or its all rapidly infused over a very short period of time.

I did not mention – I should have in my opening comments – we have not seen this type of reaction during the current set of cases associated with other types of heparin use such as slow infusions where a bolus dose was not utilized or in other situations such as heparin flushes or in indwelling catheters.

These have primarily been in dialysis centers where large doses of heparin are administered just before the patient goes under the hemodialysis machine to avoid clotting the blood in the dialysis filter. They've also been seen in cardiovascular surgery where patients go on cardiopulmonary bypass and again, you have to give large doses of heparin to prevent the blood from clotting while it's in the bypass machine.

And we've seen it also in some specialized settings called photophoresis, where blood components are being harvested by removing a patient's blood and harvesting different types of cells and then you reinfuse the blood back into the patient. That's the setting where most of these cases have occurred and those are the settings where you tend to get high bolus doses.

(Cheryl Townsend): Okay. Excuse me. For the follow-up, the bolus dose, you're referring to say, over five or ten minutes?

John Jenkins: Yes. Generally, the bolus dosing occurs fairly rapidly, but I think there have been cases where it's been over, you know, a more prolonged period of time but certainly less than an hour where large doses have been infused in short periods of time. We're not talking here about heparin infusions where, you know, a continuous dose is administered over 24 hours or so. This is the additional loading dose type of situation.

(Cheryl Townsend): Thank you.

Karen Riley: Thank you. Next question, please.

Coordinator: Next question comes from (Jennifer Corbett). Your line is now open.

(Jennifer Corbett): Yeah, hi. I'm (Jennifer Corbett). I'm with Dow Jones. The question I have is just two quick questions. Again, how many serious adverse events? I thought you said 45. And then, the other question I have is how long have you been investigating the manufacturing facilities?

John Jenkins: Right. There are approximately 350 total reports that we've received to date. Approximately 40% of those on an initial review appeared to

meet the regulatory definition of serious but our review of those cases is ongoing. As far as how long has this been under investigation, we became aware of this in mid-January – or early to mid-January through reports that we were receiving from Baxter and from the Center for Disease Control and Prevention which recently published a summary of findings of their initial case series that came to their attention, I believe in December or January.

Initially, it appeared that the cases might have been isolated to nine batches or lots of Baxter heparin. And on January 17, of this year, Baxter issued initiated a recall of those 9 lots. However, after that recall, the reports continued to come in and included reports for other lots of Baxter heparin beyond the 9 lots that had been recalled.

It's only been in the last week or so that the magnitude of the number of the reports has become clearer and during that time we've been working with Baxter to better understand the situation and to evaluate the best path forward from a public health perspective of whether we should recall the product or whether we should leave it out for use in medically necessary situations with caution.

(Jennifer Corbett): Okay, thank you.

Karen Riley: Thank you. Next question, please.

Coordinator: (Matt Perrone), your line is now open.

(Matt Perrone): Hi, yeah. I'm (Matt Perrone) with Associated Press. I just wanted to ask, this announcement, it seems like it only applies to the multiple-dose vials. I mean, are there single-dose vials and can you talk about

how those are used differently and why those aren't affected by this action?

John Jenkins: Yeah. First of all, the suspension of manufacturing is for the multiple-dose vials manufactured by Baxter. As I said, Baxter also makes single-use vials and they're continuing to manufacture those. Single-use vials are normally not used to administer the high bolus dosing that seems to be associated with the adverse events but as I noted, there have been a few cases reported where healthcare providers have taken multiple single-use vials and combined them to get the dose necessary to give a large bolus dose.

So the problem is not isolated just to the multiple-dose vials. We have seen a few cases in the single-use vials. They are not being affected right now by the manufacturing suspension because single-use vials are not normally used for the high bolus dosing where we've seen the problem.

(Matt Perone): Okay.

John Jenkins: The multiple-dose vials tend to have higher concentrations of heparin per milliliter of fluid and they – the vials themselves contain a very large amount of heparin which allows them to be used for multiple patients. So for right now, the suspension relates to the multiple-dose vials. The caution in providing bolus dosing applies to all Baxter heparin.

(Matt Perone): I see. And when you said that Baxter accounts for, I think, you know, half of the U.S. supply of heparin, was that heparin in general or were you referring to the multiple-dose vials?

John Jenkins: My understanding is that they apply to about half of the total heparin but about 75% of the multiple-dose vials. Is that correct?

Man: They're about half of the total (unintelligible) split equally between them and another competitor, right down the middle for both the multi and single dose.

John Jenkins: Okay. So it's about half.

(Matt Perone): Okay, thank you.

John Jenkins: Thank you.

Karen Riley: Thank you. Next question, please.

Coordinator: Next question comes from (Jennifer Reid). Your line is now open.

(Jennifer Reid): Yes, hi. Thank you. I'm (Jennifer Reid) with the News Press in Ft. Myers, Florida. I'm wondering if you're able to tell me – we did have a death here in Ft. Myers, although it was very unclear at the time whether there was any association with heparin whatsoever. And I'm wondering if you're including that Ft. Myers case in those four deaths.

John Jenkins: Yeah, I can't discuss the individual cases because of personal privacy reasons and the cases are still under review by FDA. I would just note that we had four reported deaths in association with use of Baxter heparin. As I said at the beginning, it's unclear at this time whether there was any relationship between use of heparin and the deaths in those cases because they didn't follow the pattern where we're seeing very rapid onset of the adverse reaction after the heparin is administered. So I can't comment on a particular case…

(Jennifer Reid): …. May I ask one more quickly?

John Jenkins: Sure.

(Jennifer Reid): Do you have any idea how long you'll – Baxter will halt the manufacturing?

John Jenkins: At this point, I think it's premature to say. We need to try to understand what's causing the problem and I think until we have a better understanding, we won't know how to address and fix whatever the problem might be. So I can't speak for Baxter but I think in our view, we need to wait and identify the source of the problem.

(Jennifer Reid): Thank you.

Karen Riley: Thank you. Next question, please.

Coordinator: We have a question from (Sandra Young). Your line is now open.

(Sandra Young): Yes, hi. Thank you for taking my question. I'd just like you to at the end of this, sum it up because I missed the top of the press conference. So if you could just sum up what you discussed so far, I'd appreciate it. Thank you.

John Jenkins: Okay, we'll try to do that.

Karen Riley: (Sandra), we can – you've seen the press releases?

(Sandra Young): The press release I hadn't received one. I just got the…

Karen Riley: Okay. We can make sure that you get one.

(Sandra Young): Okay, thank you.

Karen Riley: Okay. Yeah, and we also have a replay available after this call. I'll make sure to get back to you.

(Sandra Young): Thanks.

Karen Riley: Sure. Thank you. Next question.

Coordinator: Comes from (Gardner Harris).

(Gardner Harris): Hi guys. Sorry. One last thing. This is sort of the second time that I can remember that there has been this sort of mysterious thing happening in a biotech manufacturing process. There was the Procrit problem that seemed to result from tubes. Is this – what does this – can you tell us anything about what this says about biotech manufacturing generally and what is says about the – this sort of long-term process that you guys have had trying to come up with a way of improving biotech generics?

John Jenkins: (Gardner), I would first say that I would not lump heparin, which is a extract from biologic sources, in with biotech manufacturing because when you're speaking about biotech manufacturing, most of the times you're talking about recombinant DNA technology where you're growing a protein in a source such as a bacteria or a yeast and then you're purifying a particular protein.

Heparin is not a protein. It's a complex mixture of carbohydrates, polysaccharides that's derived from a biologic source more analogous

to how we used to get insulin. Before we had recombinant insulin, we used to get insulin from pancreases from various types of animals. So you have to take that crude extract from the animals and then purify it. So it's different manufacturing.

In both cases, they are complex procedures where you're trying to isolate the component from the mixture that you're interested in and extract out the other components that you want to eliminate, such as other proteins or viruses or other microbes, et cetera. So they overlap in the sense that they require complicated, technical extraction procedures.

I don't think I can comment at this point what impact this would have on generic follow-on biologics, because as I said, we haven't identified the source of the problem and in other cases where we've seen reactions of this type, it's turned out not to necessarily be the drug substance or the drug itself. It's been the packaging, such as the rubber that's used in the stoppers in the vials. You know, very trace amounts of contaminants can cause these types of reactions when you give them in large doses intravenously.

(Gardner Harris): Thanks so much.

Karen Riley: Thank you. Next question, please.

Coordinator: Dr. (Michael Smith), your line is now open.

(Michael Smith): Yeah, hi. (Michael Smith), MedPage Today. Can you tell us what – do you have causes of death on those four cases and are they the same sorts of things that one – that you saw was a hypotension allergic response?

John Jenkins: They were all complicated cases where there were multiple factors that could've led to the patient's death. As I said, none of them fit the pattern of what we're seeing in the other cases where the reaction was very immediate after the bolus dose of heparin was administered. We're still evaluating those cases and trying to get more details.

I think two of them occurred in patients who were hemodialysis patients and two were patients with cardiovascular disease but we don't have the specifics of all of the details yet. But at this point, they did not seem to follow the pattern of an immediate reaction right after the infusion of the large dose of heparin and they're very complicated cases.

Karen Riley: Thank you. Next question, please.

Coordinator: (Elizabeth Matrecotti), your line is now open.

(Elizabeth Matecotti): Hi, from Surgery News. Could you provide any more details on the pre-treatment with corticosteroids or antihistamines? Is there a basic regimen that most healthcare professionals would use?

John Jenkins: That would have to be up to the discretion of the actual prescribing physician. As I emphasized, we don't have data that tells us that pre-treatment with corticosteroids or antihistamines might alleviate this problem. We wanted to make physicians aware of that option because in other settings such as in patients with contrast media allergies, pre-treatment has been shown to be effective.

And most importantly, the reason we included it here is there are going to be situations where use of heparin is medically necessary and can't

be deferred and the healthcare practitioner may only have access to Baxter heparin to administer to that patient. So we wanted them to be aware of the possibility that this might be something they should consider but we can't provide any specific recommendations and particularly not on dosing regimens.

(Elizabeth Mascoti): Okay. Thank you.

Karen Riley: Conference coordinator, we have time for one more question.

Coordinator: Thank you. Next questions comes from (Jennifer Reid). Your line is now open.

(Jennifer Reid): Yes, thank you. Just one other question. And you mentioned that you'll be working with healthcare providers to find alternative sources of heparin. I'm wondering, however, if you can elaborate on that a little bit more and whether you anticipate healthcare systems may have a hard time keeping up with surgical caseloads and, you know, necessary operations with Baxter helping their operations.

John Jenkins: Yes, we're working with the other approved manufacturers of heparin to investigate their ability to increase their production and how long that might take. Those efforts are still ongoing. We're also exploring with companies that operate in other countries whether they have excess capacity that could be used to source the United States market, if we were comfortable allowing those products to be imported under, an exemption from the normal approval process.

It's clear that there are going to be problems that healthcare providers are going to be facing. It's likely that individual facilities probably obtain their heparin from one source or the other and probably not

both. So, facilities that only get heparin currently from Baxter are going to face the problem of trying to find alternative sources of heparin and also deciding to proceed forward with using the Baxter heparin in certain cases and following the advice that we gave on how we might be able to reduce the risk.

We're also working with the other manufacturers of heparin to develop procedures by which they can help assure that critical needs can be met by allocating their available supply. You know, there's going to be a shortage problem in the immediate and longer term future with the suspension of the Baxter manufacturing. That's one of the factors that went into our calculus as we decided not to encourage a recall of what's currently available.

We felt it would be better from a public health perspective to try to manage the risk and leave the product available rather than to remove the product abruptly, given the medical necessity of the heparin-admitting cases. But we are in a complex situation that starts, really immediately, because facilities and physicians are going to have to decide immediately what they want to do with regard to the heparin they have on hand and start seeking alternative sources for the longer term, because as the Baxter suspension continues, the availability of heparin will become tighter.

(Jennifer Reid): Thank you.

Karen Riley: Okay. Well thank you for participating in today's media call

Coordinator: That concludes today's conference. Thank you for participating. You may disconnect at this time.