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Quick Pulse

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HEPARIN CONTAMINATION EXPANDS BEYOND THE U.S.

The FDA found a contaminant in some batches of the active pharmaceutical ingredient (API) used in Baxter International's recalled heparin sodium, and that contaminant is believed to have been introduced in China. German health officials also reported that they found the same contaminant in some German-made heparin used in their country, but the source of the German heparin has not yet been released, so it is not known if that contamination originated in China.

FDA Commissioner Dr. Andrew von Eschenbach stressed that the contaminant has not been conclusively identified as the root cause of the heparin allergic reactions and deaths but was "associated" with more than 700 adverse events and perhaps 19 deaths in the U.S. In Germany, fewer than 100 serious adverse events have occurred, mostly if not exclusively in dialysis patients, but no deaths.

Dr. Janet Woodcock, the FDA's deputy commissioner for scientific and medical programs, chief medical officer, and acting director of the FDA's Center for Drug Evaluation and Research (CDER), said, "We are worried about this contaminant in the world heparin supply."

The FDA and German investigations are continuing, and FDA officials said there are still many unanswered questions, including whether the introduction of the contaminant was accidental or planned. FDA officials said that tests on the only other FDA-approved heparin on the U.S. market for bolus use – produced by APP Pharmaceuticals from U.S.-sourced API – did not show any trace of the Baxter contaminant.

What makes this contaminant unusual is that it mimics heparin, so it cannot be picked up with conventional purity or identity testing; it requires special testing. The finding of this contaminant has implications for every pharmaceutical company with FDA-approved drugs, not just those manufacturing in China.

Following the German discovery, the FDA recommended tests that manufacturers and regulators *worldwide* can use to screen for this contaminant. At this point, this testing is just a "request" from the FDA, but it is likely that in the future pharmas will have to boost their contaminant testing of all products to some extent, not just heparin products.

Right now, all U.S. API and finished product heparin manufacturers – even if only small quantities of heparin are involved – are being asked by the FDA to test their products with capillary electrophoresis and nuclear magnetic resonance spectroscopy. However, Dr. Woodcock reiterated that the APP heparin has tested free of the contaminant; it is other U.S. manufacturers that are being told to do the new tests, "There are many different types of heparin on the U.S. market – for IV

flushes and other uses. We would like all manufacturers of heparin to test their heparin products as well as their API to be sure there isn't this contaminant – from smaller volumes to large mass use of heparin (the bolus IV use). We would like all manufacturers to be testing their heparin."

Background

Baxter Healthcare first noticed an increase in allergic-type reactions to its multi-dose heparin in late December 2007 as part of its normal pharmacovigilance. A Baxter official said, "Allergic reactions with heparin are not unusual, but we were concerned with the increases in a short amount of time. We conveyed that information to the FDA and immediately began looking for causes. In January, we initiated a voluntary recall, and subsequently we suspended production. In early February, as additional adverse event reports continued to come in, we discussed expanding the recall with the FDA. Both of us were concerned with adequate supply to the U.S. market if the recall expanded, and it was determined that it was better to leave it (on the market, but)…to be used with caution in critical situations."

On February 11, 2008, the FDA issued a public health advisory that severe allergic reactions had been associated with Baxter's multiple-dose vials of injectable heparin sodium. The active ingredient in the Baxter heparin came from a Scientific Protein Labs (SPL) plant in China that the FDA had accidentally never inspected. Rather, they inspected the wrong plant. The FDA launched an investigation and issued a public health advisory warning healthcare professionals to watch for signs of adverse reactions to Baxter's heparin and to report those events to the FDA, but they did not order a product recall because of concerns that there was not enough product available from the only competitor to serve the market for this medically-necessary drug. However, the Chinese plant ceased production, and no new product was shipped.

A Baxter official estimated that, before the latest FDA warning, it supplied about half of the 200,000 doses of heparin given daily in the U.S., accounting for ~$30 million in sales, making it a relatively small product line for Baxter.

On February 28, 2008, the FDA announced that Baxter was voluntarily recalling all of its multi-dose and single-dose heparin as well as its Hep-Loc and Hep-Flush products. The only Baxter heparin-containing products that remained on the market were large volume parenteral solutions containing 200 Units of heparin per 100 cc in 500 and 1000 cc total volume bags. Rear Admiral Sandra Kweder, MD, deputy director of the FDA's Office of New Drugs in CDER, said the FDA still had not determined the root cause of the problem, but the recall was now possible because the FDA has been assured that the other U.S. supplier, APP, could now supply the whole market. She said, "We concluded with Baxter that a recall (on February 11, 2008) would have resulted in an immediate and severe shortage of this medically-necessary drug…so it was in the interest of public health for the vials to remain on the market but to be used with caution. Since February 11, the FDA drug shortage team has been working closely with APP, the other heparin supplier, to determine their manufacturing capacity…APP is now adequately able to supply the U.S. market…so Baxter can and is recalling all of its multiple-dose vials and single-dose vials."

As part of the recall, Baxter sent out more than 30,000 overnight letters to patients and 132,000 letters to clinicians notifying them of the recall and giving them return instructions. A Baxter official said that the decision to expand the recall was voluntary and "had nothing to do with FDA's inspection of the China plant. The recall decision was made well before the FDA concluded its inspection of the SPL China plant."

At the time of the recall, FDA officials did not believe there was substantial Baxter heparin inventory still in the pipeline. An official said, "The way Baxter produced heparin – the time between production and the time it reaches a facility – there is not a lot of inventory...It tends to get used and reordered very quickly. They stopped production February 11 (2008), so much of the product they had is mostly used up at most institutions, and they (institutions) have not been able to order any more…Our understanding is there isn't as much to recall today as would have been the case on February 11th, and distribution sources have been ramped up substantially by APP…We have a drug shortage team that works closely with manufacturers to understand the flow. As in any recall, there may be small pockets where it might be more difficult (to get heparin), but APP has been working to be sure there are no gaps in supply…And Hep-Loc and Hep-Flush have seven manufacturers that can fully supply the market."

The FDA emphasized that the Agency still has a "team" in China investigating the problem. But that team is actually just ***two people***, a "national expert in drug manufacturing technology" and a PhD with "in-depth knowledge of the manufacturing and heparin process" and who speaks fluent Chinese.

The FDA released a redacted copy of the Form 483 inspection report which found several problems in the API plant in China, though those problems had not been directly tied to the heparin adverse event issue. The observations related to:

- Deficiencies in steps to remove impurities.
- Out of specification results.
- Issues related to waste material flow.
- Deficiencies on equipment.

As of February 28, 2008, the FDA had 448 reports of adverse events associated with heparin, and reports of 21 deaths, but only four were thought directly linked to the Baxter heparin. Now, the FDA is saying there may be as many as 19 deaths.

The FDA has worked closely with the Chinese government, but one problem is where the active ingredient was obtained – from consolidators and numerous workshops and farms

upstream of the API plant in China. FDA officials declined to say how many workshops were involved, but officials said the FDA is working with the Chinese government to identify them and noted that the FDA doesn't have regulatory authority over those workshops. Michael Rogers, director of the FDA's Division of Field Investigations in the Office of Regulatory Affairs, said, "As you start going further upstream, you are dealing with intermediaries. We will go where the investigation takes us, but it requires cooperation from a number of parties, including the Chinese government and related parties…As you go further upstream from the process side to the consolidators and even further upstream, the FDA's regulations and criteria we use to assess the production coming out of those firms become difficult. We will continue to work with the Chinese government to better understand their oversight of these facilities." Dr. Murray Lumpkin, deputy commissioner of International and Special Programs at the FDA, added, "One of the things that has been very prominent in this investigation has been the cooperation of the Chinese government."

Current extent of adverse events

According to the FDA, there have been 19 deaths and 785 serious adverse events – allergic reactions and hypotension – related to Baxter's heparin since January 1, 2007. Up to 46 deaths were reported, but the FDA has found only 19 of these related to the Baxter product. The FDA's Dr. Woodcock explained, "The (46) deaths are someone who might have used heparin, and many of them are not necessarily recent use, so right now we have evaluated the 46 reports, and since January 1, 2007, we see 19 total deaths." The FDA is still evaluating the serious adverse events to see how many of the 785 are directly related to the Baxter heparin.

However, Baxter officials debated this number, insisting that, upon further study, the FDA will find there are only 4 deaths directly attributable to their product. Peter Arduini, president of Baxter's Medication Delivery business, said, "Our number is approximately 500 adverse events, which is the number Baxter received since late September. The FDA has said there have been 19 deaths, which are not limited to specific allergic reactions…The FDA noted that just because a patient took heparin doesn't necessarily mean that the heparin caused the event, and a lot of these patients (who take heparin) are very sick and very complex patients."

Dr. Woodcock indicated that the FDA does not yet know what this contaminant could do negatively, just that it mimics heparin. Other than the allergic reactions and hypotension, Baxter officials insisted that there have been no signs of the contaminant causing any additional problems, for example, problems from patients getting lower potency heparin.

A contaminant has been identified

The contaminant, described as a "heparin-like compound," was found in 5%-20% of the Baxter product. The heparin-like compound is similar to heparin glycans, which are extremely large, complex polysaccharides. The FDA does not yet know much about this compound. Asked if the compound comes from pigs, Dr. Woodcock said that the FDA doesn't know yet.

The contaminant compound was found in the Baxter API, which is made by SPL in both Wisconsin and China, and in the finished product from Baxter's Cherry Hill NJ plant. Dr. Woodcock said, "While the FDA has not determined the root cause of the adverse events, we have found a heparin-like contaminant, that is not heparin, present in some of the active pharmaceutical ingredients (APIs) produced by Scientific Protein Labs…This contaminant is present in considerable quantities – accounting for 5%-20% of the substance tested, depending on the sample, and the amount varies from sample to sample."

The FDA does not know where in the manufacturing process the heparin-like compound was introduced; it could have been either in China or at SPL's plant in Wisconsin, but Baxter officials are convinced it was added in China. Dr. Woodcock said that the contaminant reacts like heparin in conventional identity tests, which is why such tests might not detect it, "At this point we don't know how the heparin-like compound got into the product, and we continue to aggressively investigate it. We don't yet have a direct causal link between the contaminant and the adverse effects. We know that some of the suspect batches of heparin that were causing the adverse effects have this contaminant in it, so there is an association, but there is not a direct causal link yet. And we don't know if any other heparin products used outside of the U.S. might have this contaminant."

The contaminant was discovered with "advanced laboratory testing" which included nuclear magnetic resonance spectroscopy and capillary electrophoresis performed by the FDA, Baxter, and academic labs. An FDA official said that "other tests" were also important to the identification of the contaminant but refused to identify those other tests. Dr. von Eschenbach said, "We've gone beyond what is standard and usual to highly sophisticated testing to find a difference (between heparin lots containing the compound and compound-free lots) and track that difference." Baxter's Arduini said, "(Current standardized tests) were unable to detect the cause of the differences in the API. Until we get to the root cause, we won't know what test we need to screen out the differences, but the current test is not designed to detect this issue."

Asked if there might be a similarity to last year's pet food supply which was found to be contaminated with melamine, Dr. Woodcock said, "It is possible, but we don't know whether the (heparin-like) compound inadvertently got into the supply or was actually added."

The German situation

German authorities have found serious adverse reactions with heparin used in Germany and have initiated a recall of one brand – Rotex Medica GmbH Arzneimittelwerk's Heparin Rotex Medica.

Dr. Woodcock could not – or would not – say where the API in the German heparin came from except to say it was ***not*** obtained from SPL like the Baxter product; rather, it was obtained from another API supplier entirely. Dr. Woodcock said a U.S. supplier/source was not involved, but she refused even to answer whether or not she knew if China was involved, commenting, "Our discussions with other regulatory authorities sometimes have to be held confidential."

There were <100 serious adverse events but no deaths in Germany. FDA officials would not discuss any link to China. Dr. Woodcock said simply, "We were notified by German drug regulatory authorities that they have recalled heparin manufactured by a German company that fits the profile of the adverse events we saw here in the U.S…They identified a cluster of events at a dialysis center…They also have other reports where they don't have the specific manufacturer but have a cluster of similar reports from doctors."

Baxter continues its own investigation

The FDA inspected the Baxter Cherry Hill facility from January 17 to February 28, 2008, and Baxter officials said the plant passed the inspection. The FDA reportedly found no problems and issued no Form 483s.

Baxter officials said they believe that all the adulterated heparin came from China. Arduini said, "We received product from SPL's China and Wisconsin plants…We looked at specific lots of heparin associated with adverse events…We tested the API process in China and the API process in the Wisconsin plant. In both cases, the crude heparin material came from China. Using sophisticated tests such as nuclear MR, we found the same results in API in both plants. API in both plants had the same peaks…That tells us one of two things: Either the problem lies further back in the supply chain, or something in the processing before it comes to Baxter."

Ray Godlewski, vice president of quality for Baxter's Pharmaceuticals and Technology within Medication Delivery business, said that SPL has a number of tests in place to assure the safety of crude heparin, and the API is tested before it is shipped to Baxter. In addition to that, he said the Cherry Hill plant retests every lot to make sure it meets Baxter's standards, "Baxter requires tests above and beyond the USP (United States Pharmacopeia) standards, and it was only through advanced testing techniques that the differences… were detected." USP is the official public standards-setting authority for all prescription and over-the-counter medicines, dietary supplements, and other healthcare products manufactured and sold in the U.S.

Thus, Baxter's primary targets of investigation right now are the API and SPL. Arduini said, "Every lot of the material that comes from SPL to Cherry Hill (the Baxter manufacturing plant) we test with a battery of tests that exceeds the USP standards. After ruling those things out, the focus is much more on the API, and since we were able to do some magnetic resonance spectroscopy…what stands out, even though we don't have a casual link, goes in the direction of API."

Baxter performed its own audit of the SPL China plant in September 2007 and found seven problems, some of which were similar to those found recently by FDA inspectors. However, under its contract with SPL, Baxter officials said they cannot disclose the details of those problems. They said that they are monitoring for other, so-far unidentified problems, and so far haven't found any.

Asked about the SPL China plant audit, Godlewski said, "We are reviewing the findings from the FDA's inspection. We expect SPL will respond to the observations, and they need to be addressed, but we also need to recognize that they may not be indicative of the root cause. We made observations in (our) September audit, and SPL responded within the timeframe and are working on corrections. Audits are a snapshot in time, and it is not unusual that different audits months apart might have different findings."

Although the heparin-like contaminant has not been proven to be the root cause of the serious adverse events, Baxter officials said they believe it will indeed prove to be the root cause. A Baxter official said, "While our investigation into the root cause is continuing, there are a number of things that have been eliminated as potential contributing factors, and (there is) increased focus on other aspects of the process." Arduini said, "We are confident that we are on the right track to determine the root cause of the increase in adverse events. We moved as quickly as possible while adhering to the regulatory processes and also collaborated with FDA and SPL, and we shared our investigations with the FDA. On the investigation into the root cause of the allergic reactions, we excluded a number of (factors)."

Scientific Protein Labs (SPL)

SPL announced it was recalling its heparin API that tested positive for heparin contamination, and SPL issued a statement challenging the FDA on some points. Interestingly, SPL hired a former FDA press officer to help with the handling of this issue.

- "It is premature to conclude that the heparin API sourced from China and provided by SPL to Baxter is responsible for these adverse events."

- "FDA speculated that the source of the adverse events may be a contaminant. It is important to note that this theory is speculation at this point."
- "SPL has committed to the FDA to voluntarily remove from the market any lots of China-sourced heparin API where tests have indicated the presence of an extra signal/peak in testing."
- "SPL is notifying its customers who have received certain lots of that API material. SPL emphasizes that this voluntary action, which has been closely coordinated with the FDA, is being taken strictly as a precaution."
- "It is important to emphasize that the root cause of the heparin adverse events has not been tied to any of the agency's observations."

Baxter officials insisted that Baxter has no financial or ownership interest in SPL. Arduini said that SPL has been Baxter's supplier for 30 years, including 12 years of manufacturing in China, with more than 500 million high quality finished doses. In 2004, SPL started sourcing in China as well as in the U.S.

Baxter officials denied that they sourced heparin from China to save money. They explained that they pay the same amount for heparin that comes from China as they do for U.S.-sourced heparin, though the costs to SPL may be lower in China. An official said, "Whether we outsource from SPL and they manufacture it in China or in Wisconsin, we pay the same. They have been a very high quality supplier for years."

FDA inspections in China

Admitting that there are some "challenges and gaps" in the FDA's inspection history, Dr. von Eschenbach evaded reporter questions about the Agency's ability to inspect Chinese plants. He noted the FDA's need to balance risk and resources and repeatedly suggested that it would be a waste of FDA resources to inspect Chinese plants making products like tongue depressors, "We are taking a risk-based approach. Some (factories) producing devices like tongue depressors don't have the risk potential that require frequent inspections and may have long intervals between inspections, but where the risk is higher, the frequency of inspections might be sooner."

Asked what percentage of Chinese plants make low-risk medical devices like tongue depressors compared to high-risk products, Dr. von Eschenbach said, "I can't give you that answer specifically right off the top of my head. I think it's fair to say that we have continued to make a concerted effort at being able to define the plants we have to be addressing, specifically as it relates to China…As China registers plants making products, some are registered as simply being chemical manufacturing facilities, which would not fall under an FDA inspection blanket. Yet, we recognize the product being developed is a chemical that's turning into an active pharmaceutical ingredient, so we have to inspect that…It would be disingenuous for me or FDA to be suggesting that under every circumstance, in every case, we would be able to inspect every single production facility around the entire world that's making every single kind of medical product. So, we have to approach it in a more strategic way."

FDA officials were asked about an FDA Science Board report that said, "Millions of imported FDA-regulated products have never been inspected by the FDA and, with current appropriations, never will be." They were also asked (1) if it's true that the FDA over the past five years has inspected about 15 out of more than 700 Chinese plants producing API and finished drug products, and (2) if the FDA visits these Chinese plants at least minimally either in person or through paperwork. The FDA's Rogers responded, "It's important to note that the FDA's inspection program is driven by the product approval process." Dr. von Eschenbach added, "Inspections vary depending on what we're addressing…We recognize that the number of sites we must now pay attention to…are going to require us to address that systematically."

Rogers pointed out that in FY2007 the FDA did more than 1,000 foreign inspections – more than any other year in the history of the program.

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