ONE HUNDRED TENTH CONGRESS

U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

JOHN D. DINGELL, MICHIGAN
CHAIRMAN

November 19, 2008

Mr. Gene Dodaro
Acting Comptroller General
United States Government Accountability Office
441 G Street, N.W.
Washington, D.C. 20548

Dear Mr. Dodaro:

I write to request that the Government Accountability Office (GAO) review the management of the heparin issue by the Food and Drug Administration (FDA or agency) to determine the lessons learned from this matter --- what FDA did well and what FDA could have done better. This review should include addressing apparent discrepancies and gaps in FDA's assessment of heparin deaths that have been brought to my attention by the Minority Committee staff.

Of particular concern is that the staff has obtained information that casts a different light on FDA's public statements about heparin deaths, which were publicized in a broadcast of ABC's Nightline on July 30, 2008, and in the Chicago Tribune on July 30, 2008 (see Attachment A). According to the Chicago Tribune article, the FDA "conclusively linked" deaths of three patients infused with heparin to a foreign substance (OCS) found in specific lots of drug manufactured by Baxter Healthcare Corporation (Baxter). The FDA said it "completed" its review of 93 death reports related to heparin that the agency received from January 2007. The same day that the article was published, representatives from Baxter contacted the FDA to get additional information on the three deaths, and FDA identified for Baxter the MedWatch reports of the three deaths. MedWatch reports are part of FDA's Adverse Event Reporting System (AERS).

However, in an October 23, 2008, response to me (Attachment B), the FDA stated that with regard to the three death reports, FDA classified the cause of death from heparin as only "possible" in two of those cases, and "unassessable" in the third case. In addition, information in the MedWatch reports casts doubt on heparin as even a "possible" cause of death. For example, in one of the two cases FDA classified as "possible," the pharmacist who submitted the MedWatch report indicated in the follow-up

information section of the report that "[t]he patient's death was determined not to be due to heparin reaction."

Baxter's pharmacovigilance unit independently investigated these three cases, obtaining additional medical record information, interviewing pharmacists and nurses, and conducting a site visit to one of the hospitals involved in these cases. Based on its own investigation, Baxter concluded death from heparin use was unlikely in all three cases. (While Baxter concluded that the three cases cited by FDA are unlikely instances of heparin being a cause of death, Baxter provided information to the staff about five cases [without lot numbers] in which the company has not ruled out heparin as a cause of death). Staff has obtained and reviewed the MedWatch reports and Baxter's pharmacovigilance unit's commentaries with regard to the three death cases.

There are other unanswered questions concerning heparin deaths. FDA reported to me that the agency received 167 heparin death reports involving serious allergic reactions between January 1, 2007, and May 31, 2008, with only 16 reports including lot numbers. Out of the 16 allergic reaction heparin death reports received by FDA with lot numbers, the only case in which FDA determined that the cause of death from heparin infusion was "probable" involved a heparin drug made by American Pharmaceutical Partners (APP). I note that APP on its website stated that "we have not seen the anaphylactic reactions reported by Baxter" and I am not aware that FDA has publicized this information. Staff requested details from FDA about the APP case as well as details about additional death reports involving heparin since May 31, 2008, but FDA has not yet provided this information. Even if FDA's assessment is correct, it is not clear whether this death report means there is a product quality problem with APP heparin or one of the rare allergic reactions to heparin (estimated by one FDA medical official to be 1 in 10,000 – 20,000 in conversation with staff). Without the additional information on these death cases, a question is raised about whether FDA has confounding or conflicting information about heparin death cases that has not been made public.

In response to Minority Committee staff inquiries, the FDA has confirmed they reviewed MedWatch reports and the Centers for Disease Control and Prevention's February 1, 2008 Morbidity and Mortality Weekly Report. FDA also made inquiries to German health authorities about heparin case reports, but FDA told staff that German officials said there were no individual case reports to provide and only aggregate information was available.

However, with regard to the three death cases that FDA claimed were caused by Baxter heparin, FDA confirmed to staff that the agency did not follow up to interview clinical staff or Baxter for further details about each of these cases. In addition, FDA told Minority Committee staff the agency did not access other databases, even though FDA has testified that such databases enhance FDA's ability to evaluate drug safety problems. While AERS has limitations in trying to establish a causal relationship between a drug and a reported event, AERS is not FDA's only tool in assessing adverse drug events. FDA has cooperative agreements with public and private health organizations that have potentially rich sources of information about adverse drug events, and FDA has other surveillance tools. Based on the available information to staff, there is a serious and potentially troubling question about whether FDA availed itself of all of its tools to conduct comprehensive surveillance of heparin deaths.

I am particularly concerned because of the high profile of heparin safety and the international attention to FDA's analysis concerning heparin deaths. The Chinese government has openly questioned FDA's heparin investigation and whether the identified contaminant in heparin is actually a dispositive factor in causing death. Heparin safety is not only a public health concern in the U.S. but in the rest of the world.

Over two years ago, the Institute of Medicine (IOM) issued a report on the future of drug safety and made substantive recommendations about steps FDA could take to improve the agency's drug safety system. FDA testified in 2007 in hearings before the Committee's Subcommittee on Health and Subcommittee on Oversight and Investigations that the agency responded to the IOM report by making changes to strengthen science, improve communications, and improve operations and management. The apparent gaps in FDA assessment and public communication about the cause(s) of heparin deaths raise questions about whether these FDA changes have actually resulted in real improvement in drug safety oversight.

While I do have questions about the adequacy of FDA's investigation and evaluation of recent heparin deaths, I emphasize that I still support FDA's actions in imposing import alerts and requiring additional testing in dealing with the heparin safety problem. My hope is that the GAO's review will determine the strengths and weaknesses in FDA's response to the heparin drug safety problem, and will make recommendations on what FDA could do better in dealing real-time with an emerging drug safety problem in the future.

If you have any questions, please have your staff contact Alan Slobodin of the Minority Committee staff at (202) 225-3641.

Sincerely,

Joe Barton
Ranking Member

Attachments

cc: The Honorable John Dingell, Chairman
Committee on Energy and Commerce

The Honorable Frank Pallone
Chairman
Subcommittee on Health

The Honorable Nathan Deal
Ranking Member
Subcommittee on Health

The Honorable Bart Stupak
Chairman
Subcommittee on Oversight and Investigations

The Honorable John Shimkus
Ranking Member
Subcommittee on Oversight and Investigations

ABC NEWS

'Pharmaceutical Companies Must Take Responsibility'

Drug Company Executive Says FDA Too Overwhelmed to Ensure Safety

By JUJU CHANG and MARY CLAUDE FOSTER

July 30, 2008—

The blood thinner heparin is one of the most used drugs in America, employed daily in hospital surgeries and for kidney dialysis patients.

But a safe supply of this critical drug fell into jeopardy last winter in a catastrophe that illuminated severe problems caused by the fact that most ingredients for American drugs now come from foreign sources. These sources are not being adequately monitored by either the pharmaceutical industry or the Food and Drug Administration.

The FDA told "Nightline" that as many as 55, or perhaps considerably more, people may have died from the contaminated heparin. So far it's only been able to definitively link three deaths to specific lots of the tainted drug.

Although so far it's only been able to definitively link three deaths to specific lots of the tainted drug. Heparin used to be primarily produced by the pharmaceutical giant Baxter, but Baxter recalled its entire stock, nearly half the nation's supply, after the deaths from contaminated heparin. A number of smaller companies also recalled supplies. To date, Baxter says they have received 955 reports about contaminated heparin in 2008.

That's when billionaire pharmaceutical executive Dr. Patrick Soon-Shiong and his company American Pharmaceutical Partners (APP) stepped in with a large, safe supply of the drug. Without it, countless more Americans would have died.

"How would all these thousands of dialysis patients have dialysis? What would happen to all these surgeries?" Soon-Shiong said. "I have no idea; it's very scary to have thought."

Soon-Shiong has called for the reform of how the pharmaceutical industry polices its products. The companies must take a greater role, he argues, because the FDA is simply overwhelmed.

Heparin Horror

No one knows that better than Leroy Hubley. He says his wife of 48 years, Bonnie, died from a severe allergic reaction after taking contaminated heparin at a Toledo dialysis clinic.

"The doctors recommended we remove her breathing tube to end her suffering," Leroy recalled in congressional testimony. "Our entire family -- our son, daughter, in-laws and grandchildren -- were all

there. Christmas music played in the background, and each one of us said our goodbyes. Then my wife of 48 years drifted away."

Hubley's nightmare didn't end there. Within weeks, he says his only son, Randy, also a dialysis patient, died after taking heparin from the same batch of the drug.

"He too developed nausea, low blood pressure, fatigue, abdominal pain and diarrhea," Hubley testified. "A week later, my 47-year-old son was dead, leaving behind three children and a grandchild." Randy also left behind his wife, Colleen Hubley, who testified before Congress.

Investigations into the deaths pointed to China, where the raw ingredient for heparin originates. According to the FDA, someone there spiked the crude heparin with a counterfeit look-alike drug to increase profit.

"I see these foreign drugs as essentially a string of time bombs," said former FDA commissioner William Hubbard. "Heparin has gone off, and there will be more until we fix the problem."

'Process Controls'

Heparin isn't the only drug that's manufactured overseas. Roughly 80 percent of all the raw ingredients for America's drugs now come from foreign countries. Soon-Shiong, who has made billions as a pharmaceutical executive, is calling for reform.

"It became very clear to me that, unfortunately, the future is that China and India will be the breadbasket of raw materials, creating the raw materials for the rest of the world," he said. "I think heparin is a prime example of where pharmaceutical companies must take responsibility"

He said the FDA must also take responsibility, "but the FDA is overwhelmed," he said. Heparin may be used in high-tech medicine, but the raw material is literally hand-wrung from pigs' intestines in crude agricultural workshops. And the process is virtually unregulated.

"There is no process controls at the farmer level," Soon-Shiong said. "One has no idea what crude comes in, the source of the crude, are the pigs ill, do these pigs have any viruses. Frankly, are these pigs, even?"

Soon-Shiong says at his plant in China they track the entire supply chain, from "the live pig, the health and welfare of the pig, all the way to the slaughterhouse, all the way to the intestine, all the way into the crude heparin, all the way into the final heparin."

Prioritizing Patients

It's not the first time he has bucked his own industry. Back in 1985, when Soon-Shiong was working as a surgeon, he was poised to perform a pioneering transplant of cells from pigs to humans when he made a chilling discovery.

"We discovered a virus in pigs, and I refused to do that transplant," he said. "My investors said, You will do the transplants."

His investors later sued him for fraud, and he won in arbitration.

"I recall vividly, they said, 'You know, heroes and pioneers take risks, and all that you will suffer is a slap on the hand from the FDA.' And I said, 'No, that's not all I'll suffer. We'll put patients' lives at risk and I will not do it,'" he recalled.

Soon-Shiong's unwavering stance in the face of opposition may come from his personal biography. He grew up in South Africa under apartheid, and he had to fight to become the first nonwhite doctor in a whites-only hospital.

He later emigrated to the U.S. with his wife Michele, whose career as a television actress paid the bills while he labored in a university lab.

"I wanted to follow my dreams with regard to my science and my research," he said.

The gamble paid off. Soon-Shiong's medical prowess and business skills have made him one of the richest men in the pharmaceutical industry.

Self-Regulation

FDA Commissioner Janet Woodcock says the FDA is taking a "much closer look" at the safety of drugs that come from overseas, but the administration is woefully underfunded to safeguard America's drug supply.

Hubbard said the FDA "can only inspect less than 1 percent of imported foods and drugs. For example, [the FDA] can go to virtually none of these foreign drug manufacturers because it simply does not have the staff to do so."

"We don't have the resources to do that, nor should it be our primary responsibility," Woodcock said. She said the FDA keeps Americans safe "by holding the people accountable who are on the ground. Our inspectors can't be in every plant all the time."

In fact, the FDA never even inspected Baxter's supplier "SPL" in China because they couldn't find it.

"The plant wasn't inspected because there was a mix-up between that plant and another one," Woodcock said, "and it appeared that the plant that had been mixed up with this plant actually had been inspected, and so we felt that this plant had been inspected."

That leaves the pharmaceutical companies to police themselves. Baxter did conduct its own inspection last September and gave itself a passing grade, just months before Americans began dying from contaminated heparin.

"It is clearly our job to make sure that our therapies are safe, for which we have our own inspections and our own audits," said Baxter's chief scientist, Norbert Riedel. "But it is also the responsibility of the FDA to provide the necessary oversight and checks and balances than that is indeed occurring."

Riedel says that Baxter has formed a task force to examine the oversight process.

"We have put a team of scientists in place, and I'm chartering them with the task of asking where else could any one of our products be tampered with in this fashion," he said.

But Riedel points out that additional inspectors may not have saved any lives from the spiked heparin.

"I think the contaminant was made to be so similar to heparin that no test that we had in place and no facility inspection could have found it," he said.

A number of families, including the Hubley's, are now suing Baxter for wrongful death.

While there may be disagreement about how best to provide oversight, there is no argument in Soon-Shiong's mind.

"Some contaminant was absolutely added," he said. "But there were some ways to protect and prevent not just the additive, but to control the supply chain and catch it very early on."

Leroy Hubley might agree with the need for control when many precious lives hang in the balance.

"Now I am left only to deal with the pain of my wife and son, [knowing] that the unsafe drug was permitted to be sold in this country," he said. "The FDA and Baxter have not done their job. Somebody sure as hell didn't."

Article updated July 31, 2008.

ABCNews.com producer Katie Escherich contributed to this report.

Heparin taint tied to deaths

FDA: 3 fatalities linked to material in Baxter product

By Bruce Japsen
July 30, 2008

The U.S. Food and Drug Administration, for the first time, has conclusively linked deaths of patients infused with th blood thinner heparin to a foreign substance found in specific lots of the drug made by Deerfield-based Baxter International Inc.

In an interview Tuesday with the Tribune, the FDA said it completed its review of 93 death reports related to hepari that the agency received from Jan. 1 to March 31, a period when there was a dramatic spike in potentially deadly allergic reactions from patients who had been injected with heparin. The popular blood thinner is used widely in lar dosages, often before patients have dialysis or heart surgery.

Of 10 reports of death from severe shock known as anaphylaxis or hypotension, three of those could be traced to l numbers of Baxter products that tested positive for an animallike substance known as oversulfated chondroitin sulfate. Heparin lot numbers were not known for the other seven deaths from anaphylaxis or hypotension, so the FDA could not determine whether those 7 patients received heparin contaminated with the substance.

"We have what looks like a cause and effect in some patients," Dr. Janet Woodcock, director of the FDA's Center f Drug Evaluation and Research, said in an interview, referring to the three deaths linked to contaminated heparin. "We know that they got contaminated heparin, and they died subsequently. This is one of the final links in the chai

Baxter recalled its heparin products in February in the wake of the spike in the number of the allergic reactions. In recent months, federal health officials and Baxter believe the oversulfated chondroitin sulfate was intentionally put into the product from suppliers in China.

Baxter said it would not comment on the FDA's analysis, saying it has not been able to review it.

"We haven't seen this data and look forward to working with [the] FDA to understand this new information," said Baxter spokeswoman Erin Gardiner. "However, these findings appear to indicate what our own analysis has shown—that only a very small portion of the number of deaths reported seem to have a definitive link to heparin."

Before Baxter recalled and stopped producing heparin earlier this year, the company received heparin's active ingredient from Wisconsin-based Scientific Protein Laboratories, which manufactured the raw ingredients for Baxter's heparin at a plant in China. Scientific Protein's supply chain stretched through unregulated village workshops and farms in rural China. Heparin's active pharmaceutical ingredient is derived from pig intestines.

Earlier this year, the FDA tallied more than 90 reports of deaths and more than 1,000 adverse events associated w patients in the U.S. who had one or more allergic reactions to heparin products, including those sold by Baxter sinc Jan. 1, 2007.

After months of investigating 93 death reports from Jan. 1 to March 31, the agency Tuesday said it is able to give i most definitive evaluation. Of the remaining 83 reports, 13 were described as "potential complications of heparin use" such as bleeding; 25 cases were due to causes unrelated to heparin use such as pneumonia, sepsis and kidney failure.

"In the remaining 45 deaths, clinical information in the adverse-event reports is insufficient to specify the cause of death with clinical certainty," an FDA spokeswoman said. Woodcock added not enough information was given by providers or others who filled out the reports to make an adequate determination.

"While some of these [reports] appear definitely related [to contaminated heparin] many are still in the gray zone," Woodcock said. "We have looked over all of these death reports and a number of them were probably not related t the contaminated heparin."

Chinese health officials continue to question whether the problems may have originated elsewhere. The Chinese

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More from Bruce Japsen

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

OCT 23 2008

The Honorable Joe Barton
Ranking Member
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

Dear Mr. Barton:

On September 9, 2008, we sent a response letter addressing your staff's questions regarding heparin. After receiving the letter, Alan Slobodin requested clarification of that response. On September 19, 2008, staff from the Food and Drug Administration's (FDA or the Agency) Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology and Office of Compliance, participated in a telephone briefing with Alan Slobodin to clarify the information in that response. The enclosed information is in response to the additional questions Mr. Slobodin asked during that telephone briefing.

We have restated Mr. Slobodin's questions in bold, followed by our responses.

In how many of the 18 cases (deaths associated with a symptom of allergy/hypotension received between January 1, 2007, and May 31, 2008, for which a lot number is available) was heparin not the cause?

Additional review of the 18 cases presented in the previous correspondence revealed that two were duplicates (case numbers 10 and 17 were the same patient, as were case numbers 13 and 18). Therefore, the total number of deaths associated with a symptom of allergy/hypotension with lot numbers received between January 1, 2007, and May 31, 2008, is 16.

Each of the 16 cases was assessed by two or more FDA reviewers regarding cause of death. Attribution of death was scored qualitatively using the terms "Probable" (when reviewers deemed that heparin administration was the primary determinant of death), "Possible" (when reviewers deemed that heparin administration was implicated, but there was not enough specific information to warrant a "Probable" designation), "Unlikely" (when reviewers found a plausible alternative explanation for the death), and "Unassessable" (when reviewers found the information provided in the Adverse Event Reporting System (AERS) report was vague or non-specific regarding dates, temporal association of heparin administration, manner of death, or otherwise insufficient for assessment purposes).

The table below summarizes the assessments with pertinent clinical information. Five of the 16 cases were found unlikely to be caused by heparin, as the clinical narrative was found to plausibly support an alternative explanation. Deaths in these cases were attributed to lung cancer (case #1), cerebral hemorrhage (case #4), cardiac arrest (case #9), myocardial infarction (case #13), and cerebrovascular accident (case #16).

Summary of deaths for which lot numbers are available

Case #	AERS #	ISR #	Lot #	Company	OSCS in API	Clinical information*	Death Attribution (Cause of death)
1	6443231	5487230	67069	Baxter	No information	Lung CA; HIT; Acute renal failure	Unlikely (Lung CA)
2	6530251	5640256	107054	Baxter	Yes	MI	Unassessable
3	6533184	5600376	107064	Baxter	Yes	CABG; hypotension; thrombosis	Possible
			107066		Yes		
4	6547918	5608942	P209064	Baxter	No information	Cerebral hemorrhage	Unlikely (Cerebral hemorrhage)
5	6548437	5689215	86120	Baxter	No information	Peritoneal dialysis	Unassessable
6	6560930	5647877	107021	Baxter	Yes	CABG; hypotension; hemorrhage	Possible
7	6581092	5664154	KH02517	Amsino	No information	Breast CA; sudden death	Unassessable
			KH02552		No information		
8	6592887	5679553	27108	Baxter	No	Hypotension (temporal relationship to heparin unknown)	Unassessable
			37085		No		
			37045		No		
9	6611554	5701081	37059	Baxter	No information	Cardiac arrest	Unlikely (Cardiac arrest)
10	6617049	5708056	27020	Baxter	No	Myocardial infarction	Unassessable
			47092		No information		
11	6620565	5712974	27062	Baxter	No information	Pregnancy	Unassessable
12	6572106	5724149	107036	Baxter	Yes	CHF; ESRD	Unassessable
13	6634772	5733722	27020	Baxter	No	Myocardial infarction	Unlikely (Myocardial infarction)
			47092		No information		
14	6646644	5746382	405278	APP	No information	Apnea; ESRD	Possible
15	6646687	5746384	405278	APP	No information	Sudden death	Probable

						after heparin	
16	6611776	5701396	97081	Baxter	Yes	Cerebrovascular accident	Unlikely (Cerebrovascular accident)

CA = cancer; HIT = heparin-induced thrombocytopenia; MI = myocardial infarction; CABG = coronary artery bypass grafting; CHF = congestive heart failure; ESRD = end-stage renal disease

How many deaths have been reported to AERS after heparin administration since May 31, 2008?

Thirteen deaths of patients receiving heparin have been reported to FDA from June 1, 2008, to September 22, 2008. The fact that someone reports an adverse event does not necessarily mean that a specific drug caused the medical event or death. Reports have to be analyzed to see if there is a plausible causal association between the drug and the medical event. It is often not possible to tell in an individual case if there is a causal relationship between the drug and the medical event or death. Many patients have other serious conditions that could have caused the reported problem.

Is there evidence for other explanations of death reported after heparin administration aside from over-sulfated chondroitin sulfate?

There are many possible causes of death following heparin administration, including death related to underlying diseases or, in rare instances, death related to known side effects of heparin such as bleeding. The Agency is not currently in a position to know the cause of most reported deaths following heparin administration due to lack of detail in the reports, and has no knowledge of the cause of unreported deaths following heparin administration.

Thank you again for you interest in this matter. Please contact us if you have further questions.

Sincerely,

Stephen R. Mason
Acting Assistant Commissioner
for Legislation