ONE HUNDRED TENTH CONGRESS

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

JOHN D. DINGELL, MICHIGAN
CHAIRMAN

December 16, 2008

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. von Eschenbach:

The management of the heparin issue by the Food and Drug Administration (FDA) continues to be of great interest to me and others on the Committee on Energy and Commerce. I am writing to you to follow up on FDA's October 23, 2008, letter to me regarding heparin.

As part of FDA's October 23, 2008, response, the agency included a summary of deaths for which lot numbers are available. Of the 16 cases listed, the only case that FDA classified as a "probable" case of heparin causing death involved a heparin drug made by American Pharmaceutical Partners (APP). This listing was somewhat surprising because the heparin safety issue had involved a drug made by Baxter International and there were no known public cases of severe allergic reactions involving the APP drug. Several weeks ago, Minority Committee staff requested details about the APP case, but FDA has not yet provided details.

In the meantime, APP provided details to Committee staff about the APP "probable" case and another APP "possible" case included in the 16 cases listed by FDA (see attached letter dated December 10, 2008). The information provided by APP contradicts FDA's classifications and raises serious questions about FDA's review process regarding the cause of death in heparin cases. At this time, both APP and Baxter have offered refuting information to all cases that FDA classified as "possible" or "probable". I also note that a December 3, 2008, article in the New England Journal of Medicine entitled Outbreak of Adverse Events Associated with Contaminated Heparin," co-authored by two FDA officials, stated that "No determination of a causal association between these deaths [in FDA's Adverse Event Reporting System] and heparin administration has been reported . . .".

In light of this additional, apparently conflicting, information and other questions raised by the FDA's listing of 16 cases, please provide the following:

1. Copies of the MedWatch reports for the two APP cases and the other 14 heparin-related death cases included in the 16 cases listed.

2. Any amendment(s) to the list of 16 cases.

3. An explanation supporting FDA's attribution of death determination for each of the 16 cases.

4. An explanation of why in 11 out of the 16 cases listed, there was no information about oversulfated chondroitin sulfate (OSCS) in the heparin active pharmaceutical ingredient (API), particularly since manufacturers are required to retain samples for each lot circulating in the commercial market for a number of years.

5. The level of OSCS contamination in each lot where contaminant was found.

Your response by four weeks from the date of this letter would be appreciated. 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

Attachment

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

APP

December 10, 2008

Mr. Alan Slobodin
Minority Chief Counsel
House Energy and Commerce Committee
U.S. House of Representatives
Washington, D.C. 20515-6115

Dear Mr. Slobodin:

Thank you for your recent inquiry and interest in helping assure a safe and reliable supply of heparin in the United States. This response will address certain issues you discussed with Mr. John A. Waits at Winston & Strawn LLP, outside legal counsel to APP Pharmaceuticals, LLC, ("APP") regarding the recent heparin crisis. In particular, you requested comment from APP on a specific death case reported by the U.S. Food and Drug Administration ("FDA") in an attachment to correspondence addressed to The Honorable Joe Barton, Ranking Member of the Committee on Energy and Commerce, ("Barton Correspondence").

For the purpose of clarity, it is important to distinguish between heparin-related adverse events associated with contaminated raw material found in product recalled from other drug manufactures and adverse events related to general treatment with heparin. This extensive recall of product from other manufacturers led to a heparin crisis. APP's heparin was not recalled. In fact, APP's heparin has proven, through extensive testing, to be free of the contaminants connected to the recall and therefore should not be linked to serious adverse events associated with the heparin crisis.

Pursuant to regulations, APP reports all heparin adverse events to the FDA and since the above mentioned heparin crisis, it has filed the adverse event reports with the FDA on an expedited basis. The table attached to the Barton Correspondence indicates APP was the manufacturer of the heparin product in the adverse event reports identified in line items 14 and 15. The table attached to the Barton Correspondence does not give APP sufficient information to specifically identify the adverse event report in issue since the FDA assigned different tracking numbers to the adverse event reports from those numbers assigned by APP. However, APP was able to obtain all adverse event reports filed for the product lot number 405278 which was identified in the table attached to the Barton Correspondence. Lot number 405278 was manufactured in March 2008 and consisted of 44,740 Heparin Sodium Injection USP 30ml vials. Only two adverse event reports were filed involving lot number 405278 and detailed information follows regarding these two reports.

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Specifically APP200800395 and APP200800396 were received by APP from the same health care provider and, as in all cases, APP's medical information team evaluates the adverse event reports in order to assess and timely address any reported event until such time as a determination is made as to causality. After extensively reviewing each of the cases, APP believes that none of these cases could be attributed to allergic reactions to APP heparin caused by contaminants as in the other manufacturer's recalled product. In each case there were alternative etiologies which may have caused the result experienced by the patient.

APP2008800395 involved a 74 year-old male patient that had a past medical history which included: right pleural effusion, atrial fibrillation, end stage renal disease, anemia, congestive heart failure and pneumonia. The patient died of sudden cardiac arrest and no autopsy was performed. APP's investigation involved discussing the case with the patient's nephrologist nurse who indicated that the "patient had waited a long time to seek dialysis treatment and his levels were very high." APP was unable to obtain any further information in the matter. APP's pharmacovigilance remarks concluded: "Given the patient's past medical history, particularly that of congestive heart failure and atrial fibrillation, a causal link between heparin administration and *these events are unlikely*." (emphasis added).

APP200800396, involved an 85 year-old male patient that had a past medical history which included: end stage renal disease, congestive heart failure and atrial fibrillation. The patient was administered heparin on May 12, 2008 while undergoing dialysis treatment and experienced difficulty breathing. The patient was transported to the hospital and subsequently expired on May 15, 2008. It is not known whether an autopsy was performed. The patient had undergone previous dialysis treatments without incident. APP was unable to obtain further information in the matter. APP's pharmacovigilance remarks concluded: "Given the limited information as well as the cardiac past medical history, *it is unlikely* that the event is related to heparin administration." (emphasis added).

Each of the foregoing reports and the pharmacovigilance conclusions were submitted in a timely fashion to the FDA, so until APP received a copy of the Barton Correspondence, APP was unaware that the FDA had made a determination that was different from the conclusions submitted by APP. APP works closely with the FDA on any incident involving heparin and believes, based on its review that the table attached to the Barton Correspondence is in error with regard to the cases referring to APP's heparin.

APP's heparin supply continues to be proven safe and effective when administered properly. APP has tested all APP heparin lots dating back to January 2006, and they have shown to be free of the contaminants that were linked to serious adverse events involving heparin products from other manufacturers.

We are indebted to the FDA for the extensive work it has done to investigate adverse events in which heparin was administered, including the requirement of additional testing procedures to significantly reduce contamination of heparin products. We believe it is our

responsibility to do whatever necessary to assist the FDA's work in assuring a safe supply of heparin and other drugs that are so vitally needed by thousands of American patients every day.

Please feel free to contact me should you have any further questions.

Sincerely yours,

Richard E. Maroun
General Counsel

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