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ONE HUNDRED ELEVENTH CONGRESS

# Congress of the United States

## House of Representatives

COMMITTEE ON ENERGY AND COMMERCE

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July 22, 2010

The Honorable Margaret A. Hamburg, M.D.  
Commissioner  
The Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20903

Dear Dr. Hamburg:

We are in receipt of FDA's June 16, 2010, response to our April 30 letter concerning FDA's handling of the heparin contamination investigation. We write to follow up with you on information and five issues raised in FDA's letter.

First, we note that FDA in effect acknowledged that the agency's investigation has been inadequate and has been "severely hampered." While FDA stated that "[s]olving the question of who caused the contamination is an important issue for FDA," the agency admitted that after more than two years of investigation it still does not know who caused the contamination of heparin.

Second, the FDA described how the Chinese authorities impeded or hampered FDA's inspections and criminal investigation into the heparin contamination incident. For example, FDA noted that "[t]he Agency initiated inspections of manufacturers of crude heparin in China but was denied full access to the manufacturing and laboratory facilities and not permitted to review records." FDA also reported that it has been unsuccessful in getting cooperation from Chinese authorities to pursue the investigation beyond the API manufacturer and that "[t]his has impeded FDA efforts to obtain information regarding the activities that took place at sites other than the API manufacturer." Also, the FDA stated that it had not received any substantive information from the Chinese government and confirmed that the Chinese government has not solved the case. However, the FDA has provided somewhat different explanations in two separate letters. In a September 10, 2009, letter to Congressman Barton, the FDA stated that China's State Food and Drug Administration (SFDA) notified FDA on July 10, 2009, that the Chinese government had made no breakthroughs in its attempt to determine the *source* of the

contamination. In the June 16 letter, FDA stated the Chinese government claimed to have no breakthroughs on determining the *reasons* for contamination.

Third, the FDA did not dispute our concern about the adequacy of FDA's follow-up on leads in the heparin contamination investigation. FDA confirmed that the cases of Chongqing Imperial and Shanghai No.1 were similar: each firm purported to be a manufacturer of crude heparin but in fact each was a shell company using another unapproved, undisclosed Chinese firm as the actual manufacturer. Nevertheless, as we noted in our April 30 letter, FDA's investigations of the supply chains for these cases have not been consistent.

The Minority Committee staff has also identified two other instances where FDA had leads of suspect firms with little evidence of follow-up. In one case the FDA conducted an inspection and investigation from April 14-18, 2008, at Shenzhen Hepalink, a heparin API manufacturer. In connection with this firm, FDA inspectors wrote a memorandum dated April 25, 2008, entitled "Shenzhen Hepalink, Investigation of contaminated heparin API lots distributed to EU and Latin America." In that memo, FDA inspectors noted that Shenzhen Hepalink provided heparin to the U.S. and the European Union from qualified suppliers. Available test results showed crude heparin lots from the qualified suppliers were free of the OSCS contaminant. However, an Italian firm placed a large order for heparin in mid-2006, at a time when there were dwindling supplies of pig caused by the blue ear pig disease and when the price of pork had increased. The Shenzhen Hepalink Chairman told the FDA inspectors that the Italian firm agreed to let Hepalink use unqualified suppliers of crude heparin. Lots manufactured by Shenzhen Hepalink from October 2006 through March 2007 from the unqualified suppliers of crude heparin were found to be contaminated. As noted by the inspectors, "Hepalink admits they had made a bad mistake in using unqualified crude suppliers and a bad business decision in dealing with [the Italian firm]." Shenzhen Hepalink provided a list of the unqualified crude suppliers to the FDA. There is no available information indicating that FDA followed up to investigate the unqualified crude suppliers. Further, the FDA inspectors learned from Hepalink that two major German distributors, Helm AG and Welding, bought huge amounts of heparin from China for further distribution to other heparin manufacturers. As the FDA inspectors noted, "We were told this could present a huge logistic problem to tracking the origin of each heparin lot because these lots are purchased from different Chinese suppliers and can be commingled. Commingled heparin lots present another problem, the difficulty of tracing the workshop where the crude originated." The Minority Committee staff has found that FDA does not prohibit untraceable commingling of lots from different suppliers, and that FDA apparently allows brokers or traders such as Helm AG and Welding to hold Drug Master Files (DMFs) for imported drugs, which are typically held by a drug manufacturer. Both Helm AG and Welding hold DMFs with FDA for imported heparin.

In another inspection conducted in March 2009 covering Changzhou Qianhong BioPharma Co., FDA inspectors reviewed customer complaints going back to 2006 about OSCS contamination. However, there is no available information indicating that the FDA followed up to investigate the crude heparin suppliers linked to the contaminated lots. In addition, the FDA inspectors reported that Qianhong BioPharma did not have an import broker or commercial agent for the U.S. market and that the firm did not export any products to the U.S. market. However,

according to Chinese export data from healthoo.com, Qianhong BioPharma exported 36 kgs of pure heparin to the U.S. in 2007 and 38 kgs of pure heparin to the U.S. in 2008.

Fourth, the FDA indicated that the agency's investigation has been constrained by U.S. law and the agreement with the SFDA. With regard to confidential commercial information (such as the identities of manufacturers' customers or suppliers), FDA under its regulation can only share such information with a foreign governmental counterpart that has signed a confidentiality commitment. FDA does not have a Confidentiality Commitment from SFDA, and the agreement between HHS and SFDA does not provide for the exchange of confidential commercial information.

Fifth, the FDA did not respond to our questions about pressuring the Chinese government on the heparin contamination investigation. FDA did not answer whether there was a basis to make another request to the Chinese government for assistance in the investigation. Although FDA agreed that heparin contamination is an international issue, FDA did not answer why the FDA has not sought assistance from its international counterparts to form a coalition to get more cooperation from the Chinese government.

Since our April 30 letter, we have been told by U.S. Immigration and Customs Enforcement (ICE) that on June 18, 2008, the Chinese Ministry of Public Security (MPS) advised the ICE Attache Beijing that the heparin case did not involve a criminal violation since SFDA could not determine if OSGS caused any adverse events. On the same date, MPS verbally reported that no administrative violation would be pursued due to SFDA's ruling and the fact that heparin was produced by a U.S. company under contracted U.S. standards and solely for U.S. export. On June 18, 2008, the MPS advised the ICE Attache Beijing that the Chinese government would not be pursuing a criminal or administrative case in the heparin investigation. ICE further reported that on October 25-29, 2008, ICE Attache Beijing attended a meeting in Washington, D.C., which included representatives from the FDA to discuss issues relating to narcotics, counterfeit pharmaceuticals and other goods being shipped through express mail services. At the meeting, the ICE Attache Beijing discussed the heparin matter with the participants. We are troubled that FDA did not disclose to us or the Minority Committee staff over the last two years the fact that the Chinese government was not pursuing any kind of investigation on the heparin matter. In fact, FDA's communications with the staff left the misleading impression that while the Chinese investigation had been unsuccessful there was still an open investigation.

In addition, since June 2008, FDA helped publish an article in December 2008 that strengthened the case for the connection of OSGS to the reported serious adverse events. There is no evidence that FDA followed up with the Chinese government after this article and the adoption of the new U.S. Pharmacopeia Standard on heparin to challenge the Chinese government's premise for closing the investigation. FDA also conducted several heparin-related inspections in China after June 2008, but it encountered impediments in some of these inspections because of purported open Chinese government investigations of the heparin matter. Based on what has been reported to us, we presume by the fall of 2008, the FDA knew the Chinese government was not pursuing any investigation on the heparin matter. But there is no

evidence that FDA followed up with the Chinese government to get access to information, documents, and facilities that were previously off limits because of an ongoing investigation.

In light of the concerns we have outlined, please provide the following information and responses to questions within four weeks from the date of this letter:


1. Please provide all records of communications between the FDA and the Chinese government (with English translations of the Chinese government communications) relating to heparin since January 1, 2008.
2. Please provide all records of communications between the FDA and the U.S. Department of State or any U.S. embassy relating to heparin since January 1, 2008.
3. Please provide all records of communications between the FDA and its field offices in China relating to heparin since January 1, 2008.
4. Please provide all records of communications between the FDA and any of its international counterparts relating to heparin since January 1, 2008.
5. Will the FDA seek assistance from other federal agencies, including the U.S. Department of State, in gaining more cooperation from the Chinese government on the heparin contamination investigation?
6. Will the FDA seek assistance from other foreign governments in an effort to gain more cooperation from the Chinese government?
7. Please provide all records of heparin-related FDA inspections conducted in China since September 1, 2009, including the Form 483s, the establishment inspection reports, and the attachments.
8. What actions is FDA taking to protect the integrity of the drug supply from untraceable commingling or pooling of lots from different suppliers? Is clarification of FDA's extraterritorial jurisdiction over foreign drug manufacturers and suppliers needed? Are drug manufacturers required to qualify suppliers? Should drug brokers or traders hold Drug Master Files?
9. How is FDA addressing the problem of confused heparin terminology we identified in the April 30 letter?
10. Will FDA seek a Confidentiality Commitment from the Chinese government or seek an amendment to the Agreement to provide for the exchange of confidential commercial information?
11. When did the FDA first learn that the Chinese government was not pursuing any investigation on the heparin matter, and who at FDA knew? Why didn't FDA follow up with the Chinese government with new analysis that strengthened the causal

connection between OCS and the adverse events? Why didn't FDA follow up with the Chinese government to get access to information, documents, and facilities that were previously off limits because of an open Chinese government investigation?

12. Will the FDA follow up with the Chinese government to reopen the investigation into the heparin matter or gain the cooperation of the Chinese government to provide access to information, document, and facilities that would aid FDA's investigation of the heparin contamination matter?

Your prompt attention to this request is appreciated. If you have any questions, please contact Minority Committee staff at (202) 225-3641.

Sincerely,



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Joe Barton  
Ranking Member



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Michael C. Burgess  
Ranking Member  
Subcommittee on Oversight and Investigations

cc: The Honorable Henry A. Waxman, Chairman

The Honorable Bart Stupak, Chairman  
Subcommittee on Oversight and Investigations