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April 30, 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:

It has been two years since the FDA linked deaths and serious allergic-type reactions in the United States to heparin (a blood-thinning drug) that came from the People's Republic of China and was contaminated with overly sulfated chondroitin sulfate (OSCS). Unfortunately, the case of who contaminated the heparin remains unsolved.

We are very troubled by how FDA has handled the investigation to find out who was responsible for the contamination of heparin. Our concerns are based on the preliminary findings of the Minority Committee staff (staff), which has been examining the heparin contamination issue since the summer of 2008. Here are our concerns:

1. FDA has not adequately followed up on specific and credible information linking Chinese heparin firms to counterfeit heparin or contaminated heparin in several different supply chains.
2. FDA inspected several Chinese heparin firms in 2008 and 2009 for regulatory compliance issues, but did not conduct these inspections consistently and adequately for determining the source of the heparin contamination.
3. FDA has not adequately followed up with the Chinese government about the heparin contamination-source investigation. These concerns are discussed in more detail below.

1. Case Study on FDA Lack of Follow-up: Chongqing Imperial Bio-Chem. Co., Ltd.

The staff has learned that FDA has specific and credible information about certain Chinese heparin firms that warrants further investigation as suspect entities responsible for contaminating the heparin supply. However, the available information does not indicate that FDA has adequately followed up on these specific and credible leads. For purposes of this letter, we discuss the case study of Chongqing Imperial Bio-Chem. Co., Ltd. as an example of this concern.

a. Test results and investigative reports raise concerns.

There is specific and credible information to warrant further investigation of Chongqing Imperial for direct involvement in, or knowledge about, the contamination of heparin. That information is as follows:

1. According to an April 2008 internal FDA document, Chongqing Imperial provided crude heparin to Celsus Laboratories, a company based in Cincinnati, Ohio that manufactures crude heparin into an active pharmaceutical ingredient (API) and distributes the API to other dosage-form manufacturers for further processing. Three crude heparin samples from identifiable lots provided by Chongqing Imperial tested positive for OSCS contamination.
2. According to an April 2008 internal FDA document, tests showed OSCS contamination in two lots sourced from Chongqing Imperial to a non-U.S. heparin API manufacturer. These results are consistent with information the firm provided to staff that Chongqing Imperial provided two lots of crude heparin in April and May of 2007 that were subsequently found to be out of specification in November 2007 and ultimately determined in February 2008 to be contaminated with OSCS.
3. A drug manufacturer submitted data to FDA in 2008 showing the company received a crude lot manufactured by Chongqing Imperial on November 5, 2007, that was contaminated with OSCS.
4. According to a November 2008 internal FDA memorandum, a foreign regulatory agency described by FDA as a “respectable regulatory government agency” shared a “significant finding” with FDA that a Chinese heparin firm, Shanghai No. 1 Biochemical and Pharmaceuticals Co., Ltd., “sent crude heparin to the USA, which was claimed to be manufactured by them, but was actually manufactured by Chongqing Imperial and determined to be counterfeit product by [the foreign agency].”
5. Australia’s Therapeutic Goods Administration reported in June 2008 that New Zealand Pharmaceuticals (NZP) received OSCS-contaminated batches in two intact drums of heparin. The contaminant was concentrated at the bottom of the drums, whereas the top of drum samples did not contain detectable levels of contaminant.

This suggests that the OSCS was not mixed or blended into the heparin and thus the OSCS was introduced at the last step of handling. Staff learned that Shanghai No. 1 was the purported manufacturer of the heparin shipped to NZP. However, after a regulatory agency confronted Shanghai No. 1 about the contamination of this heparin, Shanghai No.1 reportedly became uncooperative and denied the heparin in question was from its lots/batches, despite Certificates of Analysis on Shanghai No. 1 stationery. A credible source about this matter told staff that Chongqing Imperial was identified as the export company/agent that shipped the heparin material to NZP.

6. According to an internal April 2008 document, the FDA had test results from a European API manufacturer that showed OSCS contamination of one crude lot sourced from Chongqing Imperial.
 - b. Public information raises questions.

There is public information that raises concerns about Chongqing Imperial. For example, Chongqing Imperial's English language website shows that the firm is located in Chongqing, with several telephone numbers and a fax number in China. However, its web address is www.canimperial.com a web address for Canimperial Biopharma Inc., a Canadian company located in Vancouver, British Columbia. This Canadian company is described in an internet listing for the Natural Products Insider Buyer's Guide as "a leading Chinese producer and supplier of vitamins, . . . animal extracts [including heparin, chondroitin sulfate, chitosan], enzymes, . . . amino acids . . . and nucleic acids . . ." The contact and marketing manager for both Chongqing Imperial and Canimperial is Richard Yin. Canimperial appears to be located at a residential address, and the phone and fax number are listed under the name Huaijun Yin (Richard Yin's Chinese name). We also note that both Chongqing Imperial and Canimperial use the same email address. In addition, Richard Yin's contact information is a Yahoo! email address created in the United States. Canimperial does not have a website. These items raise questions of whether Canimperial is a bogus front company, and whether it is used as a transshipment point or other reasons for Chongqing Imperial's exports.

There is other information in the public domain that raises questions about Chongqing Imperial. According to the website for HuaiAn MDC Chemistry Co., Ltd., Chongqing Imperial is one of its two shareholders. The website states that HuaiAn MDC is "the only one producer with a GMP facility in China who can produce high purity chondroitin sulfate for pharmaceutical industry." Staff has also learned that HuaiAn MDC has a pending Drug Master File with the FDA for "heparin sodium (crude) as manufactured in Jiangsu Province, China," which has not been reviewed by the FDA according to FDA records. The question is raised whether the ownership interest could be used as a way for Chongqing Imperial to export some of HuaiAn's crude heparin under a Chongqing Imperial label or a label of another Chinese heparin firm. It also raises a question of whether Chongqing Imperial could export under a HuaiAn MDC label.

c. Export reports raise questions.

Non-public Chinese export data reveals Chongqing Imperial's questionable patterns of exports in 2007 and 2008. According to a report by the Chinese drug information company called Healthoo.com (a company that collects data on drug sales and prices from Chinese customs offices and is considered authoritative by Western businesspeople), in 2007 Chongqing Imperial ranked as the third-leading Chinese exporter of crude heparin with 3,341 kilograms exported at an average price of \$1,159 per kilogram. The U.S. was the leading export destination at 1,600 kilograms. In 2008, according to the Healthoo report, Chongqing Imperial was ranked as the third-leading Chinese exporter of crude heparin with 4,199 kilograms at an average price of \$2,418 per kilogram, with Uruguay as the leading destination country with 1,859 kilograms and the U.S. second with 1,150 kilograms. The value of Chongqing Imperial's exports of crude heparin went from \$3,873,097 for 2007 to \$10,152,334 for 2008.

In 2007, according to a Healthoo report, Chongqing Imperial ranked as the sixth leading Chinese exporter of pure heparin with 4,205 kilograms at an average price of \$1,434 per kilogram (\$6,090,198 in value), with 475 kilograms to the U.S. In 2008, according to Healthoo data, Chongqing Imperial ranked as the seventh-leading Chinese exporter of pure heparin, with 740 kilograms at an average price of \$3,242 per kilogram (\$2,399,030 in value), with 0 kilograms to the U.S. Chongqing Imperial's reported exports of pure heparin dropped from about 56% of its exports in 2007 to only about 15%. In addition, Chongqing Imperial did not export pure heparin at all to the U.S. in 2008 and decreased its exports of crude heparin to the U.S. by about 30%, notwithstanding that the U.S. represents a very lucrative pharmaceutical market (the top average price for a major destination country, with an average price for pure heparin of \$5,626 per kilogram, over 42% higher than Chongqing Imperial's average price for pure heparin). In contrast to Chongqing Imperial, the U.S. was the lead destination export country in 2008 for the rest of the Chinese heparin industry, representing 25.5% of refined heparin exports (up from 21.62% for 2007). These changes in export patterns raise the question of whether Chongqing Imperial was either exporting to the U.S. under a different label or deliberately avoiding markets that had more focused scrutiny on OSCS starting in spring of 2008, even if those markets were much more profitable.

d. FDA's inspection report raises questions.

The FDA conducted an initial inspection of Chongqing Imperial September 22-25, 2008. (An inspector from the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) was also present during the inspection.) The FDA's establishment inspection report (EIR) notes that Chongqing Imperial was set up as a small trading company in 2002 and that its two main products are crude heparin sodium and chondroitin sulfate. An exhibit provided by the firm to the inspectors claimed that the plant was "not GMP facility," but after some debate the firm conceded it was subject to GMPs (good manufacturing practices). (The firm on its website now boasts about its GMP manufacturing.) Its English language website and the address provided to FDA showed that the firm's location was in a high-rise bank building in Chongqing. However, the EIR stated that the heparin was manufactured "at their factory." "Their factory" was approximately an hour away by car at a factory allegedly called "Chongqing Paiqiang Agri-byproduct Co. Ltd., 158 Gulongpo, Yudong, Chongqing, China." The EIR states

that the FDA inspectors obtained their translations exclusively from Richard Yin, President of the Corporation.

There is reason to question whether the FDA inspectors were misinformed about both the true identity and control of the Chongqing manufacturing site. First, the inspected site had a different company name from Chongqing Imperial which should have raised questions. We note that FDA imposed an Import Alert against Chongqing Imperial on March 16, 2009, on “All APIs” for human and animal drugs. (In fact, the FDA Cincinnati District Office refused a shipment of crude heparin from Chongqing Imperial on March 10, 2009, based on drug GMPs and adulteration violations, six days before the alert was posted.) Also on March 16, the FDA imposed the same Import Alert against “Chongqing Paiquiang Agribyproduct” (the address information is slightly different on the Import Alert from the inspection report with a listing of “158 Gonglongqing,” not “158 Gulongpo,” and no mention of Yudong). FDA’s Import Alerts treated Chongqing Imperial and Chongqing Paiquiang as different companies, as opposed to issuing another Import Alert to Chongqing Imperial with the address of the manufacturing site. That approach was taken when FDA imposed Import Alerts on another heparin firm, Shanghai No. 1, for both its corporate headquarters address and its manufacturing address. Moreover, the fact that the site had a different company name from Chongqing Imperial should have raised questions. There is no other information available in the EIR that indicates any questioning or corroboration of the claim that this was indeed a Chongqing Imperial factory. Thus, the available information in the EIR and FDA’s handling of the Import Alerts suggests that “Chongqing Paiquiang” is an alternate manufacturing site, and not actually part of the Chongqing Imperial company.

Second, staff could not verify the information on, or the existence of, Chongqing Paiquiang Agribyproduct Co. A comprehensive search, including through Chinese search engines, was conducted. Staff found that “paiquiang” has no Chinese equivalent. Other possible alternatives were tried, without success. There is no “Gonglongqing” road, but there is a Gonglong road in Chongqing.

The EIR and FDA’s Import Alerts also raised additional questions about Chongqing Imperial’s credibility. According to its website, Chongqing Imperial put out a press announcement on October 14, 2008, that FDA had inspected and approved its heparin sodium facility. However, FDA did not approve. Instead, FDA found objectionable conditions during the September 22-25, 2008, inspection, issued a Form 483 report, ultimately posted an Import Alert against the firm, and refused shipment.

2. Inspection Issues Raised by FDA’s Handling of Chongqing Imperial

In fairness to the FDA inspectors, conducting inspections in remote areas of China is very difficult and challenging. FDA inspectors have difficulty accessing the facilities and understanding the language spoken at the facilities they are there to inspect, thus relying heavily on translators from the company, an inherent conflict of interest. The EIR does not reflect that the FDA inspectors were informed of much, if any, of the information about Chongqing Imperial detailed in section 1 of this letter. The EIR does not reflect that determining the source of the

heparin contamination was a priority. In that context, we note that the EIR for Chongqing Imperial raised the following concerns about the quality of FDA's inspection: (a) FDA did not adequately investigate leads on heparin contamination, (b) FDA was inconsistent in doing traceability investigations at the Chinese heparin firms, and (c) FDA was confused about how to classify the heparin product being made in the inspected factory. Examples of these concerns are discussed below.

a. Inadequate follow-up on leads

Staff found three issues in the EIR that the FDA inspectors tried unsuccessfully to pursue or were not pursued at all. First, there may have been investigative leads from the complaint files. Chongqing Imperial received five complaints about OSCS-contaminated crude heparin produced in 2007. The FDA investigators wrote in their EIR that all complaints reviewed (four out of the five) were handled adequately by Chongqing Imperial. There was no detail provided about how the handling was adequate. Moreover, the EIR showed only that the FDA inspectors were focused on the adequacy of the handling of the complaints, not on the nature of the complaints. It is not known from the EIR what kinds of investigative leads on OSCS contamination were presented by the complaints or whether those leads were pursued by FDA.

Second, there were investigative issues with Chongqing Imperial's supply. It appeared from the EIR that Chongqing Imperial relied on a supply chain of "Casing Houses" for its source of heparin and that the FDA inspectors concluded these entities "appeared to be subject to some level of GMPs [Good Manufacturing Practices regulated by FDA]." The FDA inspector, on page 18 of the EIR, wrote the following: "It is suggested that an inspection team be sent to the Casing Houses." Staff believes from the context of the EIR that the inspector was referring to an inspection team from FDA. However, there is no indication from the available information that an FDA inspection team was ever sent to the Casing Houses. Indeed, the FDA inspectors unsuccessfully attempted to get access to the Casing Houses. According to page 16 of the EIR, the FDA inspectors requested that Mr. Yin try and obtain permission for them to visit one of the Casing Houses (not owned by the firm). According to the EIR: "He seemed reluctant to do this and later reported that his attempt to receive permission was unsuccessful."

Third, there were issues raised by Chongqing Imperial's statements regarding its brokering activities. The EIR stated on page 3 that Chongqing Imperial acts as a broker for sales of purified heparin USP for three firms in the Chongqing area. These products are sold under the manufacturer's labels and are only brokered. According to the EIR: "The firm does not repackage of [sic] relabel any of these items." However, the EIR does not address whether Chongqing Imperial repackaged or relabeled crude heparin from other firms. The EIR does not address whether inquiries were made about whether Chongqing Imperial acted as a broker for sales of crude heparin.

b. Inconsistency on traceability

The FDA conducted heparin investigations at Shanghai No. 1 Biochemical and Pharmaceuticals Co. and Chongqing Imperial in August and September 2008, respectively. Both

investigations occurred under a similar set of circumstances— both companies held themselves as manufacturers of heparin products. With respect to the Shanghai No. 1 supply chain, FDA later learned that another heparin firm, Qingdao Jiulong Biopharmaceutical Co. (QJBC), actually made the crude heparin for Shanghai No. 1, which was shipped with Shanghai No. 1 labels to the U.S. It appears this may have been similar to the situation with Chongqing Imperial's so-called manufacturing site called Chongqing Paiquiang, which FDA Import Alerts listed as if it were a separate manufacturing company from Chongqing Imperial.

FDA's investigation of the supply chain traceability was conducted much more intensively with regard to QJBC's supply chain. During the initial inspection of QJBC in July 2008, the FDA investigators found that QJBC distributed its heparin sodium to Shanghai No. 1, which then shipped the product to the United States. We note that the FDA inspectors not only included a list of the names and addresses of QJBC's crude heparin suppliers, the inspectors obtained a list of the unqualified crude heparin suppliers and the associated heparin sodium lots. In contrast, while the FDA inspectors obtained a list of vendors to Chongqing Imperial, there is no indication they checked or were able to check whether these vendors were qualified and whether there were any lots associated with unqualified firms.

Further, the FDA conducted another inspection of QJBC in November 2009. In this inspection, the FDA looked at the inadequacy of QJBC's investigation into OSCS contamination of heparin and QJBC's failure to take appropriate measures, following the heparin crisis and FDA's prior inspection, to ensure the traceability of crude heparin raw material used to manufacture its heparin product. In contrast, FDA did not conduct another inspection of Chongqing Imperial or Chongqing Paiquiang, did not examine whether Chongqing Imperial's investigation of its contaminated heparin lots was adequate, and did not check on Chongqing Imperial's ability to ensure the traceability of crude heparin raw material.

In the second inspection of QJBC, FDA noted the firm's failure to recall heparin lots shown to be contaminated with OSCS. In contrast, although Chongqing Imperial was linked to several different contaminated heparin samples in completely different supply chains, Chongqing Imperial told the FDA inspectors that "[t]he firm has not recalled any of its products in the past two years." It does not appear that the FDA inspectors raised any concerns about why Chongqing Imperial had not recalled any heparin lots even though the FDA had test results showing Chongqing Imperial had shipped contaminated heparin lots to Celsus Labs in the United States, for example.

c. Lack of clarity on terminology

The EIR raised serious questions about what heparin product Chongqing Imperial actually manufactured and/or about the FDA inspectors' understanding of the nature of the heparin product that was the focus of their inspection. According to the summary section of the EIR (page 1), this inspection was conducted as a current GMP inspection of this "Active Pharmaceutical Ingredient manufacturer." However, the EIR on page 3 indicated that the firm makes crude heparin sodium, but only acts as a broker for sales of purified heparin sodium USP provided by three other firms in the Chongqing area. (Thus, purified heparin, the equivalent of

heparin API, is treated by the FDA inspectors as distinct from the crude product.) On the same page of the EIR in the jurisdiction section, it is noted that the firm manufactures and ships “one API intermediate, Crude Heparin Sodium.” These differences in heparin terminology on just one page of the inspection report reveal much confusion over classifying heparin product. According to FDA’s expert on heparin interviewed by staff, there is no such thing as an “intermediate” with respect to heparin. Until the product reaches the API manufacturer, the material is called “crude heparin” throughout the workshop and consolidator processing stages. Thus, terminology such as “crude API manufacturer” would be an oxymoron, and the concept of an “API crude heparin intermediate manufacturer” makes as much sense as calling something “raw, partially processed, finished material.”

3. Chinese Government impediments

To the extent that the FDA has attempted to investigate the heparin supply chain in China, it has conducted these efforts mostly without the assistance of the Chinese government. FDA will never be able to get complete access to witnesses and evidence on its own in a foreign country such as China. Indeed, FDA’s legal ability to conduct a drug supply chain investigation in a foreign country is murky and as a practical matter is very limited. Indeed, as you noted in your December 8, 2009, letter to Senator Tom Carper concerning the importation of prescription drugs, “FDA does not have clear authority over foreign supply chains.” The Chinese governmental authorities are the only realistic alternative to getting any accountability for the heparin contamination that FDA believes is linked to deaths and serious adverse events in the United States.

a. Examples of Chinese government restrictions on FDA investigation

In several cases, the 2008-2009 FDA inspections of Chinese heparin manufacturing facilities were constrained by Chinese authorities. Three examples are the inspections of Hangzhou Ruihua Biochemical Products (HRBP), Changzhou Qianhong Biopharma Co (CQBC), and Yantai Dongcheng Biochemicals Co. (YDBC). In each example, after the FDA became aware of restrictions by Chinese authorities, staff did not find or receive any evidence that the FDA followed up with the Chinese government to raise concerns about these restrictions. Moreover, even if FDA’s position was to defer to the restrictions imposed at the time, there is no indication that the FDA revisited these issues with the Chinese government at a later time.

First, on the last day of the HRBP Establishment Inspection, the General Manager of HRBP stated that the local police instructed him not to allow the FDA inspection to go any further. He further stated that he could no longer allow the FDA inspectors to walk through the HRBP lab or see any documents. The FDA then concluded the inspection.

Second, one year prior to the FDA’s inspection of CQBC, China’s State Food and Drug Administration (SFDA) sealed numerous heparin lots in CQBC’s possession. Because these samples were sealed, CQBC was unable to conclusively identify them as contaminated heparin, and their supplier remained on the Approved Crude Heparin Supplier List. The sealing of these

lots prevented the FDA inspectors from determining whether these lots were contaminated, and, if contaminated, conducting a traceback investigation for the source of the contamination.

Third, after YDBC received five complaints of contaminated heparin in 2008, it notified the SFDA, who in turn ordered YDBC not to open any of its retained heparin samples. Later SFDA went to the firm and sealed the cabinets where the samples were kept. Thus, FDA could not determine whether the samples were tainted. In both the second and third examples, there was no suggestion in the EIR that the FDA sought confirmation from the Chinese authorities on why the samples were sealed or whether they could be unsealed. Staff has no information indicating whether the FDA has ever followed up with the SFDA concerning these samples.

b. FDA has a basis under its agreement with the SFDA to renew a request for Chinese investigation of the source(s) of heparin contamination.

In December 2007, FDA and the SFDA entered into a memorandum of agreement on the safety of drugs and medical devices. The purpose of this agreement is to facilitate the exchange of information between the governments and enhance the safety of Chinese imports to the U.S. In addition, FDA recently opened permanent offices in Beijing, Shanghai, and Guangzhou, China. Thus, FDA has an agreement and staff in China to facilitate communication and cooperation on the investigation of heparin contamination.

Several provisions in the agreement obligate a party to investigate harm caused to the other party by drugs and medical devices exported from the party's territory. Article IV(D)(2)(e) requires each party to "to enhance cooperative activities with its appropriate law-enforcement and regulatory authorities to actively investigate and prosecute individuals or entities that manufacture, sell, distribute, handle, test, trade, or export misbranded, adulterated, or Counterfeit Drugs" Since contaminated heparin is an adulterated drug, China is obligated to cooperate with the U.S. on an investigation of contaminated heparin. But the terms "adulterated" and "cooperate" are not expressly defined in the agreement. "Drug" is defined to include "active pharmaceutical ingredients." In addition, Article IX(E) states that "The Parties shall endeavor to resolve any dispute regarding the implementation or interpretation of this Agreement through timely consultations." Thus, this agreement provides a framework for FDA communication with the SFDA and the Chinese government about the investigation of the source of heparin contamination.

In light of the concerns we have outlined about FDA's investigation of the source(s) of heparin contamination, please provide the following information and responses to questions within four weeks from the date of this letter:

1. What is FDA's strategy for solving the question of who caused the contamination of the heparin supply? Please detail the strategy and when it was developed, the names and positions of the FDA officials who developed the strategy, and the names and positions of the FDA officials responsible for implementing the strategy.

2. To what extent can FDA conduct a traceability investigation of various heparin supply chains in China on its own without the assistance of the Chinese government?
3. Assuming FDA could solve the case on its own, what would FDA do with this information?
4. What actions is FDA taking to follow up on the Chongqing Imperial issues raised in this letter?
5. Does the FDA agree there is a basis to make another request to the Chinese government about the heparin contamination investigation? If not, why not?
6. Is the FDA willing to cooperate and even share information with the Chinese government in an effort to solve the heparin contamination case? Would FDA be able to do this under current law and under the current agreement with the SFDA? If not, why not?
7. Does FDA agree that the contamination of the heparin supply is an international issue? If so, why hasn't the FDA sought international support from the World Health Organization and/or other countries to get more transparency and cooperation from the Chinese government, or to provide assistance to the Chinese government, in the heparin contamination-source investigation?

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

Sincerely,



Joe Barton
Ranking Member



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