DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
9200 Corporate Blvd
Rockville, MD 20850

Certified Mail
Return Receipt Requested

APR - 8 2008

IMPORTANT NOTICE

TO MANUFACTURERS AND INITIAL DISTRIBUTORS OF MEDICAL DEVICES THAT MAY CONTAIN HEPARIN OR ARE HEPARIN-COATED

The Food and Drug Administration (FDA), Center for Devices and Radiological Health (CDRH) wants to inform you of important information relating to heparin products and to seek your immediate action.

The FDA has been notified of a number of serious adverse events potentially related to contaminated heparin. Several recalls have also occurred as a result of contaminated heparin. The contaminated crude heparin and heparin active pharmaceutical ingredient (API) appear to be originating from more than one source. To date at least one contaminant has been identified as oversulfated chondroitin sulfate.

It is your responsibility under 21 CFR 820.50 and 820.80 to have purchasing controls and acceptance activities that provide reasonable assurance of the safety and effectiveness of your device. We are writing to alert you of a new safety risk that demands immediate attention and possible elevation of your purchasing controls and acceptance activities to assure device safety.

ACTIONS TO BE TAKEN BY MEDICAL DEVICE MANUFACTURERS AND INITIAL DISTRIBUTORS

The CDRH is concerned about the safety and effectiveness of medical devices that may be affected by this contaminant, and the possible effects the contaminant may have on the accuracy of in-vitro diagnostic assays. Because of these concerns, we ask that all device manufacturers and initial distributors of heparin containing or coated products assure that their products are contaminant-free. Specifically, we urge that all imported lots of heparin sodium API be tested by laboratories capable of performing the FDA recommended test methods described below.

Specifically, CDRH recommends that you:

1. Determine which specific product(s) you manufacture or distribute in unfinished or in final form that contain heparin or utilize heparin in their processing. If you have no such product then no further action is needed.

2. If you manufacture or distribute ANY product that contains heparin or is heparin coated, it is important to ensure that the heparin has been shown to be contaminant-free using the test methods described below before the product is released.

- There are two tests to detect contaminated heparin: the nuclear magnetic resonance (H-NMR spectroscopy) and capillary electrophoresis (CE) tests. For more information about these tests, please see the agency's heparin web page: http://www.fda.gov/cder/drug/infopage/heparin/default.htm (see "Screening Methods"). These tests are to be conducted only on the heparin sodium active pharmaceutical ingredient (API). There is currently no test to detect the contaminant for a finished medical device and the current United States Pharmacopeia (U.S.P.) monograph for heparin will not detect this contaminant. As more testing information becomes available, we will update our heparin web page.

3. If any lot of heparin API used in your product is determined to be contaminated or otherwise linked to a contaminated lot, you should evaluate your product for possible recall and take the appropriate action, as required by 21 CFR 820.90, 820.100 and 820.198, and as described in http://www.fda.gov/ora/compliance_ref/rpm/chapter7/ch7-5.html and 21 CFR 806 Corrections and Removals. If action is needed, alert your FDA District Office if you are a domestic manufacturer or distributor. If you are a foreign manufacturer you should alert CDRH, Office of Compliance, at the telephone number provided below.

4. In accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.53, FDA requests that manufacturers submit to us, within five (5) work days of becoming aware, all reports of any adverse reactions related to the use of heparin that have or may have caused or contributed to a death, serious injury, or reports of malfunctions in which the malfunction of the device or a similar device would be likely to cause or contribute to a death or serious injury if it were to recur. Heparin-related adverse events may include, but are not limited to, allergic/hypersensitivity reactions, unexplained thrombocytopenia, excessive anticoagulation/hemorrhage, unexplained or premature catheter/device thrombosis, unexplained hypotension or acute dyspnea, or spurious results of in-vitro diagnostic tests that utilize heparin either as part of the assay or as part of the specimen collection.

   This request for 5-day reports becomes effective as of the date of this letter and will remain in effect for duration of 120 days (21 CFR 803.53). You must submit the 5-day reports (and any, supplements to the initial reports, responses to Additional Information (AI) letters, etc.) to our MedWatch program using one of the following two methods:

   1. Paper Submissions: Please mark the envelope containing your submission with the term "5-Day Report." In addition, please mark the "5-Day" box in element 7 of Section G on the 3500A form itself. Forms should be mailed to: Food and Drug Administration, CDRH, Medical Device Reporting, P.O. Box 3002, Rockville, MD 20847-3002.

   2. Electronic Submissions: Please refer to the enclosed attachment for details on how to submit your report(s) electronically.

   If your firm is currently authorized, per section 803.19, to submit adverse event reports under CDRH's Alternative Summary Reporting (ASR) program, please note the following:

   - Your authorization to submit heparin-related reportable events in your summary report is suspended for the time period defined above and you must submit these events as 5-day reports (section 803.53);
   - You must submit any heparin-related reportable events on the MedWatch Form 3500A, per sections 803.52 and 803.53 of the MDR regulations.

To assist us in learning as much as possible about this situation, it would be very helpful if you would include the following information in your MDR reports, if available:

- A description of the patient's underlying disease/disorder and the reason for use of the device;
- A list of the patient's concomitant medications and allergies;
- The concentration and total amount of heparin on/in the device;
- The nature of the adverse event and the interventions required to address it;
- An explanation of why you believe the heparin component of the device was responsible for, or contributed to, the adverse event;
- The timing of the adverse event in relation to use of the device; and
- Whether systemic intravenous heparin or subcutaneous heparin was administered during, or in proximity to, use of the device (and if so, the concentration and total amount given).

If some of this information is not available at the time you submit your 5-day report, but is available at a later time after further investigation, please submit it as a supplement to your original report.

5. If you have noted quality problems with your heparin raw material or if you have any information that you would like to provide to the FDA, please contact CDRH Office of Compliance by telephone at 1 (866) 751-5262 or by FAX at 240-276-0114.

BACKGROUND INFORMATION

Heparin is an anticoagulant (blood thinner), which is intended to decrease the clotting ability of blood. In January 2008, Baxter Healthcare Corporation initiated a recall of nine lots of heparin sodium injection multi-dose vials. (See website information at: http://www.fda.gov/oc/po/firmrecalls/baxter01_08.html.) These vials were distributed in two sizes: 1000 units/mL in 10 mL vials and 1000 units/mL in 30 mL vials. Baxter recalled these lots because of an increase in allergic-type adverse events associated with the use of Baxter heparin sodium for injection. Symptoms may include: abdominal pain, chest pain, increased heart rate, shortness of breath, fainting, unresponsiveness, decreased blood pressure, vomiting, wheezing, and throat swelling. No dose-response curve has been established, so it must be assumed that any amount of contaminant in the heparin could cause adverse effects.

In early February 2008, after learning about an increase in adverse events involving the Baxter heparin product, FDA launched an investigation in the United States and abroad. This included inspecting Baxter's domestic facilities, determining the distribution of heparin in the United States from all known sources, and sending a team of experts to China to conduct a comprehensive inspection of Scientific Protein Laboratories LLC.'s (SPL) Changzhou, China manufacturing facility that makes the active ingredient for Baxter's drug, and for other customers.

In February 2008, Baxter expanded the recall to include all lots and all sizes of its multi-dose vials of heparin sodium injection, as well as single dose vials, and its heparin lock flush products after additional reactions to heparin were reported. (See http://www.fda.gov/oc/po/firmrecalls/baxter02_08.html.)

In March 2008, SPL (http://www.spl-pharma.com), located in Wisconsin, recalled lots of their heparin API that were distributed to a number of medical device manufacturers. Products made from those lots are adulterated by the contaminant. Additionally, B. Braun announced a recall of lots of heparin supplied by SPL.

To obtain more information on the heparin recalled product, you may visit the FDA Public Health Advisory website at the FDA web site http://www.fda.gov. If you have any questions concerning the contents of this letter, please contact Ms. Betty W. Collins, Director, Division of Enforcement A, Office of Compliance at 240-276-0115.

Sincerely yours,

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices
and Radiological Health

Enclosures:

Electronic Reporting for Heparin related MDRs

Introduction

CDRH's electronic Medical Device Reporting (eMDR) program is a voluntary program with two options for electronic reporting, accommodating both low and high volume reporters. Visit www.fda.gov/cdrh/emdr for complete information on CDRH's eMDR program. The purpose of this document is to provide reference information on electronic reporting for Heparin related events.

Submitting Heparin related MDRs electronically

To submit your Heparin related MDRs electronically, we recommend using the low volume eMDR option, called CeSubmitter or CeSub, unless you have already used the high volume option for regular MDR submissions. The CeSubmitter option is a free downloadable application that allows the submission of MDR reports one at a time. The software provides the MedWatch 3500A form data elements and generates an electronic MDR and is particularly suited for quick set up and reporting. The following pointers will help you set up for electronic reporting.

Notification of participation

If you choose to submit your Heparin related MDRs electronically please send an email to eMDR@fda.hhs.gov. Please provide the following information –

(1) Subject line should read –electronic reporting of Heparin related MDRs
(2) Please provide a contact name, phone number and email address for all inquiries regarding electronic submissions.

FDA Gateway

(1) eMDR utilizes the FDA Electronic Submissions Gateway (ESG), an agency-wide entry point for all electronic submissions, to receive electronic MDRs. The Gateway authenticates and validates electronic submissions and routes it to CDRH. Please visit http://www.fda.gov/esg/ for more information. To establish an account with the FDA ESG, please visit http://www.fda.gov/esg/ESG/account.htm
(2) If you have MDRs related to heparin that you need to submit while you are working to set up your account, please email your electronic MDRs to cMDR@fda.hhs.gov
(3) Once you establish an account with the FDA ESG, and complete an initial test, you will then use the ESG account to submit your electronic MDRs. At that time, you no longer need to email your MDRs to the eMDR mail box.

CeSubmitter

(1) Visit http://www.fda.gov/cdrh/cesub/eMDR_technical.html to access the CeSub software and technical information.
(2) You may install the software on your local hard-drive or a network drive in your organization
(3) The software allows you to submit 5-day, initial, and follow-up MDRs –
    a. For 5-day MDRs, please select '5-day' for type of report in G7
    b. For initial MDRs, please select 'initial' for type of report in G7
    c. For follow-up/supplemental MDRs, please select 'follow-up' for type of report in G7

d. For responses to Additional Information letters, please select 'Response to FDA Request' in H2, and select 'follow-up' for type of report in G7. Using CeSubmitter, you may attach the AI letter from FDA, in the attachment area after section H10.

(4) CeSubmitter allows you to send attachments. See attachment area after section H10.
(5) Follow the instructions for entering your information into the form.
(6) Once you complete entry of your information, on the top menu bar, select Output→package files for submission. CeSubmitter will generate a zip file with your MDR and attachments, if any.
(7) Submit the zip file via the FDA ESG Gateway, or while you are working to establish an account with the FDA ESG, email your submission to eMDR@fda.hhs.gov

Testing

Electronic MDR submissions normally go through a testing process to ensure that the file formats are correct and that data is being loaded accurately into CDRH systems. We recommend two test files, submitted sequentially – an initial MDR and a follow-up MDR with an attachment. However, if you have reports which must be submitted now, please follow the steps above and email the submission to us. If you presently have no reports to submit, but anticipate such reports in the future, we recommend you follow the test pointers below to facilitate quick processing of Heparin related MDRs.

(1) Please send an email to eMDR@fda.hhs.gov to indicate you are testing
(2) Send the electronic file you are using for testing to eMDR@fda.hhs.gov account.
(3) If you have an established ESG test account, send your test submission through the gateway
(4) If you are working to set up an ESG account, send your test submission to the eMDR@hhs.fda.gov mail box.
(5) Send your initial MDR. Once you get notification from us that the file loaded successfully to our test systems, you may submit the follow-up MDR test.

For all questions related to electronic reporting, please email eMDR@fda.hhs.gov.