Update to Healthcare Facilities and Healthcare Professionals about Heparin and Heparin-containing Medical Products

The Food and Drug Administration is summarizing important information relating to medical products that contain potentially contaminated heparin and is seeking assistance from healthcare facilities and providers in identifying and reporting adverse events related to these products.

Recommendations and Considerations

- Be aware of recent recalls of injectable heparin and heparin flushes and of life-threatening reactions which have been reported in association with contaminated heparin. Current recall information is available at http://www.fda.gov/cder/drug/infopage/heparin/default.htm#recalls and will be updated when new information becomes available. Additional information on reported adverse events can be found at http://www.fda.gov/cder/drug/infopage/heparin/adverse_events.htm.

- Report any adverse patient reactions that may be associated with injectable heparin and heparin lock flush solutions. In addition, we are asking you to report heparin-related adverse reactions associated with use of other medical products which contain or are coated with heparin. This includes a wide variety of medical devices and diagnostic products as described below. Instructions for reporting these adverse events are also provided below.

Background on heparin and heparin-containing medical products

Heparin is an anticoagulant (blood thinner) that is commonly administered intravenously or subcutaneously. It is used in patients undergoing kidney dialysis, certain types of cardiac surgery, and treatment or prevention of other serious medical conditions, including deep venous thrombosis (DVT) and pulmonary emboli. These products are typically sold in concentrations of 1000 U/mL or greater. Heparin lock flush solutions, which are generally used to maintain the patency of intravenous catheters and are considered to be medical devices, are manufactured at concentrations of 100 U/mL or less.

A variety of other medical devices and diagnostic products may also contain or be coated with heparin, including certain intravascular catheters, oxygenators, pumps, filters, and blood reservoirs used during cardiac procedures, vascular stents/grafts, and blood collection tubes. A list of specific medical devices containing heparin is provided at http://www.fda.gov/cdrh/safety/heparin-device-list.html. This is not an inclusive list of all firms that manufacture or distribute heparin-containing devices or a complete list of medical devices that contain or are coated with heparin. This list will be updated as additional information becomes available.

Adverse Events, Product Recalls, and FDA Actions

There has been an increase in the number of adverse events, including deaths, reported in association with the use of injectable heparin products. In particular, FDA has seen an increase in events consistent with an anaphylactic-type reaction and/or acute hypotension. Information on these events is available at http://www.fda.gov/cder/drug/infopage/heparin/adverse_events.htm. To date, only a small number of similar events have been reported for heparin lock flush solutions.

FDA scientists have identified a contaminant in the heparin – an oversulfated chondroitin sulfate. The contaminant mimics heparin activity so closely that it was not recognized by routine testing. FDA now has in vitro and animal data demonstrating a solid mechanistic link between the oversulfated chondroiton sulfate and the adverse events observed after bolus dosing. Our data demonstrate that the compound directly activates the kinin-kallikrein pathway in human plasma, which can lead to the generation of bradykinin (a potent vasoactive mediator) and C3a and C5a (potent anaphylatoxins). These data were recently published in the New England Journal of Medicine.

Several manufacturers and distributors of heparin products have initiated recalls of their products based on reports of adverse events associated with their product(s) or as a precaution after testing revealed that they were supplied with contaminated lots of heparin. Further information on these recalls may be found at http://www.fda.gov/cder/drug/infopage/heparin/default.htm#recalls.

The Center for Drug Evaluation and Research (CDER) has received commitments from the major US heparin manufacturers/suppliers to perform the recommended screening tests on all heparin active pharmaceutical ingredient (API) that is received (http://www.fda.gov/cder/drug/infopage/heparin/default.htm#screening). In addition, FDA's Center for Devices and Radiological Health (CDRH) has issued a letter requesting medical device manufacturers and distributors to determine if they market unfinished or final form products that contain heparin or utilize heparin in their processing, and if so, to ensure that the products are contaminant-free before they are released for distribution (http://www.fda.gov/cdrh/safety/heparin-notice.html).

Reporting Heparin-Related Adverse Events

FDA continues to actively monitor its post-market safety database for cases of heparin-related adverse events. Because we believe that it is essential to learn of new events as soon as possible, we are asking you to report any

significant adverse events that may be *heparin-related*, whether the product is a drug or a heparin-containing medical device.

In particular we are asking you to report:

- events with signs or symptoms consistent with anaphylactic-type reactions, acute hypotension, and/or acute gastrointestinal distress.
- any other serious reaction which may be attributed to the heparin in a medical product. These may include, but are not limited to
    - unexplained thrombocytopenia;
    - excessive anticoagulation or hemorrhage;
    - inadequate anticoagulation;
    - unexplained or premature thrombosis of a heparin-coated device; or
    - spurious results of in-vitro diagnostic tests that utilize heparin either as part of the assay or as part of the specimen collection.

To assist us in learning as much as possible about the adverse events, please include the following information in your reports, if available:

- The specific name of the product and its manufacturer;
- The lot number of the product;
- A description of the patient's characteristics, co-morbid conditions, and the reason for use of the product (diagnosis);
- A list of the patient's concomitant medications, therapies, and allergies;
- The route of administration, concentration and total amount of heparin given or on/in the device;
- The nature of the adverse event, the interventions required to address or correct it, and the clinical outcome;
- The time to event after heparin administration or device use;
- An explanation of why you believe the injectable heparin drug or the heparin component of the medical device was responsible for, or contributed to, the adverse event; and
- In the case of medical devices, whether systemic or subcutaneous heparin was administered concomitantly along with the device (and if so, the concentration and total amount given).

Please submit your reports to FDA as follows:

Healthcare providers should report adverse events to the FDA's MedWatch Adverse Event Reporting program either

- online at www.fda.gov/medwatch/report.htm;
- by returning the postage-paid Voluntary Form FDA 3500 (available in PDF format at www.fda.gov/medwatch/getforms.htm) to 5600 Fishers Lane, Rockville, MD 20852-9787;
- by faxing the Voluntary Form FDA 3500 form to 1-800-FDA-0178; or
- by reporting the event by phone at 1-800-332-1088

User facilities such as hospitals and nursing homes are required to report suspected medical device-related deaths to both FDA and the manufacturer, if known, and medical device-related serious injuries to the manufacturer or to FDA, if the manufacturer is unknown. Again, please note that heparin lock flush solutions and in vitro diagnostic tests are considered medical devices and are therefore subject to these reporting requirements. These reports must be made on the MedWatch Mandatory Form FDA 3500A (available at www.fda.gov/medwatch/getforms.htm). Reports should be sent to Food and Drug Administration, CDRH, Medical Device Reporting, P.O. Box 3002, Rockville, MD 20847-3002.

Although user facilities are not required by law to report drug-related adverse events to FDA, we are asking that when you become aware of any such event related to use of a heparin injectable drug, you submit a Voluntary Report Form FDA 3500 directly to us. You can obtain the form at www.fda.gov/medwatch/getforms.htm. These reports should be provided to FDA using the methods described above for **healthcare providers**.

If your facility participates in **FDA's Medical Product Safety Network (MedSun)** program, please submit your reports for both device and drug-related heparin reactions to the MedSun website, as you currently do for your device reports. MedSun will forward your heparin-related drug reports to the Center for Drug Evaluation and Research for you.