4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2012-D-0083]

Guidance for Industry on Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a guidance for industry entitled "Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality." This guidance was initially published as a draft guidance on February 13, 2012. The draft was revised to clarify FDA's expectations and recommendations and to include references to a recently-developed assay for detecting ruminant contamination of crude heparin.

DATES: Submit either electronic or written comments on Agency guidances at any time.

ADDRESSES: Submit written requests for single copies of this guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 2201, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the guidance document.

Submit electronic comments on the guidance to http://www.regulations.gov. Submit written comments to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Frank W. Perrella, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 4257, Silver Spring, MD 20993-0002, 301-796-3265; or Dennis M. Bensley, Jr., Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Pl., Rockville, MD 20855, 240-276-8268; or Scott McNamee, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, rm. 3416, Silver Spring, MD 20993-0002, 301-796-5523.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry entitled "Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality." This guidance provides recommendations that will help active pharmaceutical ingredient (API) manufacturers, pharmaceutical and medical device manufacturers of finished products, and others, to prevent the use of crude heparin that might contain oversulfated chondroitin sulfate (OSCS) or non-porcine material (especially ruminant material) contaminants. This guidance on crude heparin recommends strategies to test for contamination and should be used in addition to the United States Pharmacopeia (USP) monograph testing required for other forms of heparin to detect the presence of OSCS.

Following reports of serious adverse events (including deaths) among patients injected with heparin sodium in 2008, FDA identified the contaminant OSCS in crude heparin sourced from China. FDA is also concerned about the potential for contamination of heparin with ruminant materials. The control of the quality of crude heparin is important to ensure the safety of drugs and devices and to protect public health. FDA developed this guidance to alert

manufacturers to the risks of crude heparin contaminants and to recommend strategies to ensure that the heparin supply chain is not contaminated with OSCS or any non-porcine ruminant material (unless specifically approved as part of drug or medical device application).

The guidance recommends that manufacturers test and confirm the species origin of crude heparin in each lot of every shipment before use in the manufacture or preparation of a drug or medical device containing heparin. The test method should be qualified for use in testing crude heparin and for the identification of species origin. The method should be based on good scientific principles (e.g., sufficient accuracy and specificity) and possess a level of sensitivity commensurate with the current state of scientific knowledge and risk. FDA has posted a method entitled "Heparin Multiplex Real-Time PCR Assay (hMRTA)," on the Internet at http://www.fda.gov/AnimalVeterinary/ScienceResearch/ToolsResources/ucm350289.htm. This method will be updated occasionally and persons performing the assay should visit the Web site regularly to ensure they are using the most current version.

The guidance also recommends that manufacturers test for OSCS in crude heparin in each lot of every shipment before use, using a qualified test method that is suitable for detecting low levels of OSCS concentrations and is based on good scientific principles. FDA has also made an HPLC method for testing for the presence of OSCS in crude heparin available on the Internet at http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM206230.pdf. Users of this method should also review the Web site occasionally to ensure they are employing the most current version.

In addition to testing crude heparin for species of origin and the presence of OSCS in crude heparin, manufacturers should reject for use any crude heparin found to contain any

amount of OSCS, or to be derived from, in any amount, ruminant mucosa (unless approved in the drug or device application). If imported into the United States, any such crude heparin or heparin products in which it was used should be controlled, and manufacturers should notify FDA of any such finding. The guidance also recommends that manufacturers identify and audit crude heparin suppliers and heparin API suppliers to ensure conformance to appropriate quality standards. Manufacturers should employ the controls described in the guidance for industry entitled "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients" and comply with the quality system regulations (as applicable).

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the Agency's current thinking on Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

II. Comments

Interested persons may submit either electronic comments regarding this document to http://www.regulations.gov or written comments to the Division of Dockets Management (see ADDRESSES). It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at http://www.regulations.gov.

III. The Paperwork Reduction Act of 1995

This guidance refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). In the guidance, FDA advises drug and medical device manufacturers who receive and use crude heparin to manufacture drugs and medical devices to notify the Agency of crude heparin found to contain any amount of OSCS, or to be derived from, in any amount, ruminant mucosa (unless approved in the drug or device application) (for human drugs, 21 CFR 314.81(b)(1)(ii); for animal drugs, 21 CFR 514.80(b); for medical devices, 21 CFR 803.50). The collections of information in 21 CFR 314.81(b)(1)(ii) have been approved under OMB control number 0910-0001; in 21 CFR 514.80(b) under OMB control number 0910-0284; and in 21 CFR 803.50 under OMB control number 0910-0437.

IV. Electronic Access

Persons with access to the Internet may obtain the document at either http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm or http://www.regulations.gov.

Dated: June 19, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

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