Guidance for Industry

Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Frank W. Perrella at 301-796-3265, (CVM) Dennis M. Bensley, Jr., at 240-276- 8268, or (CDRH) Jason Brookbank at 301-796-5770.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Center for Devices and Radiological Health (CDRH)

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Current Good Manufacturing Practice (CGMP)

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Center for Drug Evaluation and Research
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dsmica@fda.hhs.gov

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to alert manufacturers of active pharmaceutical ingredients (APIs), pharmaceutical and medical device manufacturers of finished products, repackers, and others to the potential risk of crude heparin contamination.[2]

This guidance provides recommendations that will help API manufacturers, pharmaceutical and medical device manufacturers of finished products, repackers, and others, to better control their use of crude heparin that might contain oversulfated chondroitin sulfate (OSCS)[3] or non-porcine material (especially ruminant material) contaminants. The use or development of methods complementary to those set forth in the United States Pharmacopeia (USP) to identify and control the animal origin of crude heparin is critical to monitor and confirm the species origin of

[1] This guidance was developed by the Office of Compliance in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Veterinary Medicine (CVM) and the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration.

[2] For the purpose of this guidance, we use the term *crude heparin* to mean an unrefined mixture of heterogeneous polysaccharides including various impurities isolated from mammalian tissues that requires further purification and processing before clinical use.

[3] *Oversulfated chondroitin sulfate* (OSCS) is an over-sulfated form of chondroitin sulfate (CS) that contains an unusual type of sulfation not found in any natural source of CS. Glycosaminoglycans are polysaccharides containing repeating disaccharide units composed of alternating sulfated residues of N-acetylgalactosamine and D-glucuronic acid. Although CS is a naturally occurring glycosaminoglycan (e.g., derived from cartilage by products), OSCS is a semi-synthetic derivative of CS made by the chemical sulfonation of native CS. Thus, OSCS typically contains two to three additional sulfate groups per disaccharide unit compared to chondroitin sulfate. For the purpose of this guidance, we use the term *OSCS* to mean oversulfated chondroitin sulfate and related oversulfated glycosaminoglycan analogs.

heparin. This is consistent with the current USP monograph for Heparin Sodium (USP33-NF28 Supplement 1 Reissue), which states: "Label [the heparin sodium] to indicate the tissue and the animal species from which it is derived." The identification of the animal origin of heparin has been studied by physico-chemical, immunological, and polymerase chain reaction (PCR) methods. Notwithstanding certain limitations, these methods have the potential to detect ruminant material contaminants in porcine heparin. Some of these methods (e.g., PCR, immunochemical) could be used to monitor and control the raw materials used for quality heparin production.[4] This guidance outlines the importance of testing for contamination in crude heparin — testing that should be performed in addition to the USP monograph tests required for other forms of heparin to detect OSCS.[5]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance describes the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Heparin Contamination

In early 2008, FDA received reports of serious acute hypersensitivity reactions (including some resulting in death) in patients undergoing dialysis.[6] Further investigation as well as the sudden onset of adverse events suggested the contamination of heparin sodium for injection as a common factor among the cases. In April 2008, after extensive analysis and screening, FDA identified the contaminant OSCS in heparin API manufactured in China. A large proportion of the heparin supply is imported into the United States from foreign facilities. In the past, FDA has identified OSCS in the heparin supply, including in batches of crude heparin. In addition to the United States, at least 10 other countries reported the presence of contaminated heparin within their supply chains. OSCS contamination of heparin appears to be an example of intentional adulteration, and has also been referred to as economically motivated adulteration— i.e., heparin appeared to be intentionally contaminated with OSCS to reduce the cost of production.

[4] For the specificity of the tests, see IL FARMACO 51: 247-254 (1996); J.Pharm. Biomed. Anal. 27: 305-313 (2002); J.Pharm. Biomed. Anal. 29: 431-441 (2002); Molecular and Cellular Probes 20: 250-258 (2006); J. Food Protection 72: 2368-2374 (2009).

[5] Such testing should also include steps to monitor and confirm the species origin of heparin, as discussed above in note 4 and throughout this guidance. See discussion in section III and note 11.

[6] For further details, see Kishimoto, T., Viswanathan, K., Ganguly, T., et al., "Contaminated Heparin Associated with Adverse Clinical Events and Activation of the Contact System," N. Engl. J. Med. 2008; 358:2457-2467; McMahon, A.W., Pratt, R.G., Hammad, T.A., et al., "Description of Hypersensitivity Adverse Events Following Administration of Heparin that was Potentially Contaminated with Oversulfated Chondroitin Sulfate in early 2008," Pharmacoepidemiology and Drug Safety 2010; 19: 921-923.

Beyond OSCS contamination, the complexity and global nature of the heparin supply chain provide other opportunities for intentional adulteration. In particular, substitution of non-porcine sources of crude heparin raises concerns. Crude heparin is primarily sourced from porcine mucosa, and only heparin products produced from porcine intestinal mucosa are approved in the United States. The potential for bovine heparin substitution poses a special risk because of possible contamination with the bovine spongiform encephalopathy (BSE)[7] agent derived from ruminant materials. The control of the animal origin of crude heparin is critical to ensure the safety of drugs and devices that contain heparin and to protect public health.

Both the reported incidents of OSCS contamination and the bovine substitution scenario illustrate the potential for FDA-regulated products derived from heparin to be contaminated. Therefore, it is important for drug and medical device manufacturers to be diligent in ensuring that no component used in the manufacture of any drug or medical device containing heparin is contaminated with OSCS or non-porcine (especially ruminant) material.

As previously discussed, generally the manufacture of heparin involves the extraction and isolation of crude heparin from porcine intestinal mucosa and further purification of heparin. FDA has issued a Health Information Advisory to make the public aware of FDA's ongoing effort to monitor the safety and quality of the heparin supply.[8]

B. Regulatory Authority

Crude heparin is often intended for use as a component of other drugs, including heparin sodium for injection and low molecular weight heparins.

FDA considers the presence of OSCS or any non-porcine origin material, especially ruminant material (unless specifically approved as part of the drug application) in crude heparin, or any other form of heparin, to render that drug adulterated under section 501 of the FD&C Act (21 U.S.C. 351).

Medical devices may also contain drug components such as heparin; for example, certain medical devices may be coated with heparin. FDA also considers the presence of OSCS or any non-porcine origin material, especially ruminant material (unless specifically cleared or approved as part of a device premarket submission) in a device containing heparin to render that product adulterated under section 501 of the FD&C Act (21 U.S.C. 351).[9] Under 21 CFR 820.50 and 820.80, medical device manufacturers are required to have purchasing controls and acceptance activities to ensure that devices containing heparin meet specified requirements.

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[7] Butler, D., "British BSE Reckoning Tells a Dismal Tale," Nature 1998, 392: 532-533.

[8] Public Health Update: Recall of Heparin Sodium for Injection (2/28/2008), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm112665.htm; Follow-up Notice to Heparin Device Manufacturers and Initial Distributors (4/8/2009), http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm135352.htm.

[9] The presence of OSCS or any non-porcine origin material, especially ruminant material, in products containing heparin may also implicate other violations of the FD&C Act.

FDA requires manufacturers of drugs to monitor the identity, strength, quality, and purity of their products. (See, e.g., 21 CFR 211.100 for finished pharmaceuticals.) It is critical that a firm's quality control program ensure the safety and quality of crude heparin used to make FDA-regulated products. It is equally important that firms engage in business only with appropriately qualified suppliers.

FDA's guidance for industry, *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (ICH Q7),[10] establishes minimum expectations for proper material control in the manufacture of APIs and use of API starting materials, including, but not limited to, a supplier management program that ensures use of only qualified material suppliers.[11] Also, FDA's guidance for industry, *Q9 Quality Risk Management* (ICH Q9), provides guidance regarding the application of risk management principles to the manufacture of drugs.

For medical devices, the control of suppliers is addressed in the Quality System regulation under Purchasing controls (21 CFR 820.50). The relationship between purchasing controls and acceptance activities (21 CFR 820.80) is vital and directly related to design controls, especially the output of risk analyses and other risk management activities (21 CFR 820.30(g)) to support better decision-making and establish the type and extent of controls commensurate to the risk.[12]

[10] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[11] See ICH Q7 section VII, Materials Management.

[12] In addition to purchasing controls, acceptance activities, and design controls, there are other requirements under 21 CFR Part 820; for example, manufacturers must have procedures to control and evaluate nonconforming products (21 CFR 820.90) and implement any actions necessary to correct and prevent recurrence of nonconforming product and other quality problems escalated to corrective and preventive actions (820.100). Ultimately, manufacturers of devices containing heparin must comply with all applicable requirements under 21 CFR Part 820.

III. RECOMMENDATIONS

Because of the risk of potential heparin contamination in the future, it is important that manufacturers take steps to ensure that the heparin supply chain is not contaminated with OSCS or any non-porcine origin material, especially ruminant material (unless specifically approved as part of the drug or medical device application). FDA recommends that drug or medical device manufacturers who receive and use crude heparin to manufacture drugs and medical devices containing heparin do the following:

1. Test and confirm the species origin of crude heparin in each 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.

2. Test for OSCS in crude heparin in each 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 suitable for detecting low levels of OSCS . 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 published an assay method for measuring OSCS contamination in crude heparin using Strong Anion Exchange (SAX) high-pressure liquid chromatography (HPLC).[13] This method has been evaluated for suitability using crude heparin of porcine origin and OSCS reference materials. An appropriate alternative method or methods can also be qualified for use in screening crude heparin for the presence of OSCS.

3. Know the identity and role of the actual manufacturer of crude heparin and any repackers and distributors who handle crude heparin before receipt and use. Manufacturers of drugs and medical devices containing heparin should audit their crude heparin suppliers and heparin API suppliers to ensure conformance to CGMP.

4. Employ the controls described in ICH Q7 to prevent the use of crude heparin containing OSCS, and to fully and promptly investigate and resolve deviations and failures of quality, especially identity and purity.

[13] See "Analysis of crude heparin by ^{1}H-NMR, capillary electrophoresis, and strong-anion-exchange-HPLC for contamination by over sulfated chondroitin sulfate," J. Pharm. Biomed. Anal. 51: 921-926 (2010). This HPLC method has a limit of detection for OSCS of less than 0.1 percent. This analytical method for crude heparin is available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM206230.pdf

5. Reject for use, control, and properly dispose of any crude heparin found to contain any amount of OSCS or ruminant material contaminant, and notify the local FDA district office of the finding.[14]

[14] Applicants/manufacturers must comply with post-market requirements (e.g., 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).