# Guidance for Industry

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

**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)**

**June 2013**

**Current Good Manufacturing Practice (CGMP)**

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*Contains Nonbinding Recommendations*

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## 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 prevent the use of crude heparin that might contain over-sulfated chondroitin sulfate (OSCS)[3] or non-porcine ruminant material contaminants. It is important to monitor the use or development of test methods for crude heparin in addition to those set forth for heparin sodium API in the United States Pharmacopeia (USP). It is also important to identify and control the animal origin of crude heparin and confirm the species origin of heparin. This is consistent with the current USP

[1] This guidance was developed by 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 linear polysaccharides mainly composed of repeating units of highly sulfated disaccharides containing uronic acid, either D-glucuronic acid or L-iduronic acid, and D-glucosamine, and including various impurities extracted from mammalian tissues that requires further purification and processing before clinical use.

[3] *Over-sulfated 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 byproducts), 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 over-sulfated chondroitin sulfate and related over-sulfated glycosaminoglycan analogs.

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 detect ruminant contamination in the raw materials intended for use in quality heparin production.[4,5] This guidance outlines the importance of testing for contamination in crude heparin — testing that should be performed in addition to the USP monograph tests set forth for heparin sodium API (used to make unfractionated and low molecular-weight heparin) to detect OSCS.[6]

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.[7] 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 was then and is now imported into the United States from foreign facilities, and manufactured with crude heparin sourced from China.) 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.

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[4] For the specificity of the tests, see *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* 75: 1107-1112 (2012); *Anal. Bianal. Chem.* 404: 43-50 (2012).

[5] See "Heparin Multiplex Real-Time PCR Assay (hMRTA)." This analytical method for crude heparin is available at http://www.fda.gov/AnimalVeterinary/ScienceResearch/ToolsResources/ucm350289.htm.

[6] 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.

[7] 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 for porcine heparin generally raises concerns, unless specifically approved in a drug or medical device application. The potential for bovine heparin substitution, for example, could pose a risk because of possible contamination with the bovine spongiform encephalopathy (BSE)[8] agent derived from ruminant materials.[9] The control of the animal origin of crude heparin is important for ensuring the safety of drugs and devices that contain heparin and to protect public health.

The reported incidents of OSCS contamination, FDA's past discovery of OSCS in both heparin API and crude heparin, and the ruminant substitution scenario illustrate the potential risk of contamination for FDA-regulated products derived from heparin. 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 material.

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.[10]

## B. Regulatory Authority

As previously discussed, the manufacture of heparin generally involves the extraction and isolation of crude heparin from porcine intestinal mucosa and further purification of heparin. 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 use of any non-porcine origin material, especially ruminant material (unless specifically approved in the drug application) in crude heparin, or any other form of heparin, to render that drug adulterated under section 501 of the Federal Food, Drug, and Cosmetic Act (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 approved in the device application) in a device containing heparin to render that product adulterated under

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

[9] Scientific Opinion on BSE Risk in Bovine Intestines, EFSA Panel on Biological Hazards, European Food Safety Authority, *EFSA Journal* 2009, (1317): 1-19.

[10] 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.

section 501 of the FD&C Act (21 U.S.C. 351).[11] 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.

FDA requires manufacturers of drugs to ensure the identity, strength, quality, and purity of their products. (See, e.g., 21 CFR 211.84 and 211.100 for finished pharmaceuticals.) FDA's guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (ICH Q7)*[12] provides guidance on 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.[13] 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. 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.

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.[14]

[11] 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.

[12] In November 2005, ICH renamed *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (ICH Q7A)* as *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (ICH Q7)*. 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.

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

[14] 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 (21 CFR 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 in the drug or medical device application. FDA recommends that drug establishments that receive or use crude heparin to manufacture drug products or heparin components for use in medical devices do the following:

1. 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 (including APIs, drug products, and heparin components for use in a medical device).

The test method should be qualified for use in testing crude heparin and for the detection and identification of the species origin of ruminant material. 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 an assay method for measuring ruminant contamination in crude heparin using real-time polymerase chain reaction (PCR, hMRTA).[15] This method has been evaluated for suitability using crude heparin of porcine origin and bovine reference materials. An alternative method or methods can also be qualified for use (i.e., sufficiently validated for the degree of precision/accuracy required for its use) in screening crude heparin for the presence of ruminant material.

2. Test for OSCS in crude heparin in each lot of every shipment before use in the manufacture or preparation of a drug (including APIs, drug products, and heparin components for use in a medical device).

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).[16,17] This method has been evaluated using crude heparin of porcine origin and OSCS reference materials. An alternative method or methods can also be qualified

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[15] See "Heparin Multiplex Real-Time PCR Assay (hMRTA)." This analytical method for crude heparin is available at http://www.fda.gov/AnimalVeterinary/ScienceResearch/ToolsResources/ucm350289.htm.

[16] 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.

[17] For another assay method for detecting OSCS in crude heparin, see, Sommers, C.D., D.J. Mans, L.C. Mecker, and D.A. Keire. 2011. Sensitive Detection of Oversulfated Chondroitin Sulfate in Heparin Sodium or Crude Heparin with a Colorimetric Microplate Based Assay. *Anal. Chem*. 83: 3422-3430.

for use (i.e., sufficiently validated for the degree of precision/accuracy required for its 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 APIs, finished drug products, and heparin components for use in medical devices should sufficiently audit[18] and qualify their crude heparin suppliers to ensure conformance to appropriate quality standards.

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

5. 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 application). If imported into the United States, control and properly dispose of any such crude heparin or heparin products in which it was used and notify the local FDA district office of the finding.[19]

[18] See, e.g., CDRH Quality System Audits Medical Device Quality Systems Manual, available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/MedicalDeviceQualitySystemsManual/ucm122726.htm.

[19] Applicants and/or manufacturers must comply with relevant postmarket 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).