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Heparin-Containing Medical Devices and Combination Products: Recommendations for Labeling and Safety Testing

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Guidance for Industry and Food and Drug Administration Staff

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

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Preface

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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

1. Introduction[1]

The United States Pharmacopeia (USP)[2] drug substance monograph for Heparin Sodium, and drug product monographs for Heparin Lock Flush Solution and Heparin Sodium Injection, recently have undergone several revisions following serious and fatal events related to the use of heparin sodium products.[3] Investigation of heparin product overdose errors identified the expression of drug strength in the labels as a major contributing factor in these errors. This guidance document addresses these safety concerns by clarifying new expectations for labeling with regard to the revised heparin USP monographs,[4] as well as outlining safety testing recommendations.

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[1] The Office of Combination Products (OCP) and the Center for Drug Evaluation and Research (CDER) were consulted in the preparation of this guidance.

[2] The United States Pharmacopeial Convention is a scientific nonprofit organization that develops standards for the identity, strength, quality, and purity of drugs and drug ingredients marketed in the United States. These standards are published in the compendia, U.S. Pharmacopeia and National Formulary (USP-NF). The Federal Food, Drug, and Cosmetic Act (FD&C Act) recognizes the USP-NF as official compendia. Section 201(j) of the FD&C Act.

[3] USP Monograph: *Heparin Sodium*, USP Monograph: *Heparin Sodium Injection*, USP Monograph: *Heparin Lock Flush Solution*. The FD&C Act generally requires a drug product to conform with an applicable official USP drug product monograph. Sections 501(b) and 502(g) of the FD&C Act.

[4] See also "FDA Drug Safety Communication: Important change to heparin container labels to clearly state the total drug strength" (available at https://www.fda.gov/Drugs/DrugSafety/ucm330695.htm).

In addition, the outbreak of serious and often fatal events due to heparin contamination with oversulfated chondroitin sulfate (OSCS) in 2008 led the USP to include in its drug substance monograph additional testing of heparin sodium to ensure its quality and purity. This guidance also outlines use of conformance to the monographs in premarket submissions, namely testing specified in the current USP monographs and testing and documentation recommendations contained in the guidance document "Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality."[5,6]

Note that recommendations made in this guidance reflect FDA's current position on this issue and may change in the future as new scientific information or new detection methods become available. FDA intends to revise this guidance document as needed to reflect any additional revisions to these USP heparin monographs.

For the current edition of the FDA-recognized standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database Web site at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe 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 guidances means that something is suggested or recommended, but not required.

2. Scope

This guidance provides labeling and safety testing recommendations for medical devices and for combination products that include heparin sodium or low molecular weight heparin that have a device primary mode of action (PMOA) or are otherwise assigned to CDRH for regulation.[7] Note that some devices for *in vitro* diagnostic uses include heparin. Such products can be classified as devices if the heparin would not come into contact with the body when the product is used as intended. Products that include a device and heparin for *in vivo* use are combination products.[8] Products that include only bonded coatings of heparin sodium or low molecular weight heparins with a fixed total dose of heparin are unlikely to pose a risk of heparin overdose and recommendations in this guidance may not be warranted; however, recommendations in this guidance may be appropriate for these types of products in certain instances, such as in cases where significant amounts of heparin are found to be released.

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[5] Available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291390.

[6] The Agency updates guidances periodically. To make sure you have the most recent version of this guidance, check the FDA guidance page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[7] Center assignment for combination products is based on which constituent part (the drug or device in this case) provides the PMOA, i.e., makes the greatest contribution to the overall intended therapeutic effects of the combination product. See section 503(g)(1)(C) of the FD&C Act; 21 CFR 3.2(m). If PMOA cannot be determined with reasonable certainty, Center assignment is based on application of the criteria at 21 CFR 3.4(b).

[8] For additional information on combination products, please visit https://www.fda.gov/CombinationProducts/default.htm.

3. Background

Heparin has been identified as a high-alert medication by the Institute for Safe Medication Practices (ISMP) due to a heightened risk of patient harm when dosed incorrectly. In 2003, the USP's Safe Medication Use Expert Committee recognized a recurring trend of medication errors related to misinterpretation of the expression of concentration on the labeling of injectable products, resulting in serious consequences to patients, including death. Heparin products span a wide range of doses and concentrations based on the indication for use for the product as well as the intended patient population. Heparin administration for systemic anticoagulation is provided as final concentrations ranging from 50-100 units/mL. The source vials from which these dilutions are prepared contain concentrations ranging from 1,000-20,000 units/mL. When heparin sodium is only intended to maintain patency of an indwelling intravascular catheter, the heparin lock flush solution (which is regulated by FDA as a drug-device combination product with a device PMOA (see 71 FR 47499 (August 17, 2006)), typically includes heparin concentrations ranging from 1-100 units/mL packaged in 1-30 mL vials with total drug content ranging from 1 unit to 1,000 units or a variety of fill volumes in prefilled syringes with total drug amounts per syringe ranging from 1 unit to 500 units.

In 2007, the USP Parenteral Products-Industrial Expert Committee recommended revisions to the new "Strength and Total Volume for Single- and Multiple-Dose Injectable Drug Products" section of USP General Chapter <1> *Injections*. These revisions became official in 2009 and this information was subsequently relocated to General Chapter <7> *Labeling* in 2016. This chapter directs that for single- and multiple-dose injectable drug products, the strength per total volume should be the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength per mL enclosed by parentheses. Following these changes, FDA and ISMP expressed concern that the labeling prescribed in the Heparin Lock Flush Solution monograph (and in the Heparin Sodium Injection monograph) was inconsistent with General Chapter <7> *Labeling*. USP's Expert Committees, including the committee responsible for these Heparin monographs at that time, Monographs-Biologics and Biotechnology 1, proposed revisions to the labeling sections of the heparin monographs that would incorporate the USP standards for labeling for injectable medications, specifically, USP General Chapter <1> *Injections, Strength and Total Volume for Single- and Multiple-Dose Injectable Drug Products* (which now appears in <7> *Labeling*). Those revisions became official May 1, 2013.

4. Labeling Statements

A. For Heparin Lock Flush Solution Products

The USP monograph for Heparin Lock Flush Solution requires the product labels[9] express strength per total container volume as the primary expression of strength, followed in close

[9] Under section 201(k) of the FD&C Act, "The term 'label' means a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of this Act that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word,

proximity by strength per mL enclosed by parentheses, for single- and multiple-dose injectable drug products. The strength per total volume should be the primary and prominent expression on the principal display panel of the label.[10] For example:

Total strength/total volume:	100 USP Units/10 mL
Strength/mL:	(10 USP Units/mL)

For products containing a volume of less than 1 mL, the strength per fraction of an mL should be the only expression of strength.[11] For example;

Strength/mL:	100 USP Units/0.5 mL

For products containing a volume equal to 1 mL, the strength should be expressed as strength per mL, not strength/1 mL.

Strength/mL:	100 USP Units/mL

The Agency further recommends that the above information be included in the instructions for use as part of the device/combination product description. Consistent with the monograph, the label must identify the organ (e.g., intestinal mucosa) and the animal species (e.g., porcine) from which the heparin sodium is derived.[12]

B. For Heparin-Bonded Products

Specific labeling for the amount and strength of heparin for heparin-bonded products is not generally needed. However, there may be additional labeling considerations based on the specific device type and review of the product. For example, the Agency may recommend that the amount and strength of heparin be included in the label if significant amounts of heparin were found to be leaching from a product. In such cases, the total amount of heparin per total surface area should be displayed on the primary package label followed by the concentration per area unit in parentheses. For example:

Total amount of heparin/total surface area:	100 USP Units/total surface area^2
Strength/area unit:	(10 USP Units/unit of surface area^2)

The Agency further recommends that the above information, if requested, be included in the instructions for use as part of the device/combination product description. For all heparin-bonded products, the Agency recommends the labeling identify the tissue (e.g., intestinal mucosa) and the animal species (e.g., porcine) from which the heparin sodium is derived.

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statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper."

[10] USP Monograph: *Heparin Lock Flush Solution*.

[11] Id.

[12] Id.

5. Safety Testing for Heparin-Containing Products

Manufacturers of heparin lock flush solutions must comply with the current USP monograph for that product, as well as the USP drug substance monograph for Heparin Sodium. Manufacturers of heparin sodium injections must comply with the current USP monograph for that product, as well as the USP drug substance monograph for Heparin Sodium. See sections 501(b) and 502(g) of the FD&C Act. Firms are also recommended to follow the guidance document, "Heparin for Drug and Medical Device use: Monitoring Crude Heparin for Quality," mentioned above. [13,14] In addition, we recommend that manufacturers who receive heparin sodium drug substance or active pharmaceutical ingredient (API) that is represented to be "USP" to produce a combination product or an *in vitro* diagnostic medical device that includes heparin sodium or low molecular weight heparin ensure and document that the heparin has been tested according to the current USP drug substance monograph, and that it is manufactured and/or tested consistent with applicable guidance documents on heparin. Manufacturers of medical devices and combination products containing heparin must comply with the elements of safety testing that are required to be performed and documented as part of compliance with the Quality System (QS) regulation for devices (21 CFR 820), and with both the QS regulation and current good manufacturing practice requirements for drugs if the product is a combination product (see 21 CFR Part 4).

Premarket submissions to CDRH – premarket notification (510(k)) submissions, premarket approval (PMA) applications, De Novo requests, and humanitarian device exemption (HDE) applications – should describe the heparin product in detail and document compliance with heparin safety testing. Please note, however, that heparin testing data and records should be maintained on file with the medical device or combination product manufacturer, but do not need to be included in premarket submissions. See Appendix A for more details. The premarket submission should include the following information:

- Heparin source-tissue and confirmation of species origin (e.g., porcine intestinal mucosa);

- Identification of the actual manufacturer (i.e., name, address, and contact information) of the heparin sodium API and any repackagers and distributors who handle the heparin sodium before receipt.

The premarket submission should also provide the following to indicate the manufacturer's conformance with testing parameters from the guidance "Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality."

- Testing for OSCS using methods that are qualified and suitable for detecting low levels of OSCS concentrations (e.g., strong anion exchange high-pressure liquid chromatography and ^{1}H Nuclear Magnetic Resonance).

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[13] Available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291390.
[14] In addition, the Center for Drug Evaluation and Research (CDER) has issued a guidance for industry, "Immunogenicity-Related Considerations for Low Molecular Weight Heparin," available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM392194.

- Heparin-containing combination products and medical devices should also comply with the contaminant safety testing recommendations in the USP monograph on Heparin Sodium and the Center for Drug Evaluation and Research's (CDER's) guidance recommendations[15] to detect OSCS contamination of heparin and to identify of the animal origin of the heparin.

[15] "Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality," available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291390.

Appendix A - Documentation of Heparin Safety Testing

FDA recommends that the following Heparin Safety Controls testing data and records of crude heparin, heparin API, and heparin product be maintained on file:

- Heparin crude:
    - Procedure(s) followed to reject, 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, as well as documentation of all related actions taken.
- Heparin sodium (including heparin sodium used to make low molecular weight heparin):
    - Description of controls used to prevent the use of heparin containing OSCS or any other contaminants (e.g., USP monograph tests, ICH Q7, "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients").
    - Description of how the manufacturer followed CDER's heparin guidance, "Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality."[16]
    - Although batches of heparin sodium that have deviated from specifications, have failed testing, or that are contaminated should be rejected and not enter the supply chain, all procedure(s) followed to fully and promptly investigate and resolve deviations and failure of quality or document that the heparin sodium has been in compliance, as well as documentation of all related actions taken should be maintained on file.
- Heparin product:
    - If further manipulation of the USP heparin product in your manufacturing activities is required, documentation that this additional manipulation will not interfere with product purity or effectiveness.

[16] Available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291390.