



## **Preface**

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DRAFT

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

## Draft Guidance for Industry and Food and Drug Administration Staff

*This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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.*

### 1. Introduction

The United States Pharmacopeia (USP)<sup>1</sup> 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.<sup>2</sup> Investigation of heparin product overdose errors identified the expression of drug strength in the labels as a major contributing factor in these errors. When finalized, this guidance document will address these safety concerns by clarifying new expectations for labeling with regard to the revised heparin USP monographs,<sup>3</sup> as well as outline safety testing recommendations.

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. When finalized, this guidance will also outline use of conformance to the monographs in premarket submissions,

<sup>1</sup> 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 compendium, *U.S. Pharmacopeia* and *National Formulary* (USP-NF). The Federal Food, Drug, and Cosmetic Act (FD&C Act) recognizes the *USP-NF* as an official compendium. Section 201(j) of the FD&C Act.

<sup>2</sup> *USP37–NF32, at 3222* (Heparin Sodium); *USP37–NF32, at 3227* (Heparin Sodium Injection); and at *3228* (Heparin Lock Flush Solution). The FD&C Act requires a drug product to conform with the related official USP drug product monograph. Sections 501(b) and 502(g) of the FD&C Act.

<sup>3</sup> See also *FDA Drug Safety Communication: Important change to heparin container labels to clearly state the total drug strength* at <http://www.fda.gov/Drugs/DrugSafety/ucm330695.htm>.

67 specifically testing and documentation requirements and/or recommendations contained in the  
68 current USP monographs and the guidance document *Heparin for Drug and Medical Device*  
69 *Use: Monitoring Crude Heparin for Quality*  
70 ([http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291390.pdf)  
71 [UCM291390.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291390.pdf)).<sup>4</sup>  
72

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

77  
78 FDA's guidance documents, including this guidance, do not establish legally enforceable  
79 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should  
80 be viewed only as recommendations, unless specific regulatory or statutory requirements are  
81 cited. The use of the word *should* in Agency guidances means that something is suggested or  
82 recommended, but not required.

## 83 **2. Scope**

84  
85 This guidance provides labeling and safety testing recommendations for medical devices and for  
86 combination products with a device primary mode of action that include heparin sodium or low  
87 molecular weight heparin and assigned to CDRH for regulation.<sup>5</sup> Products that include only  
88 bonded coatings of heparin sodium or low molecular weight heparins with a fixed total dose of  
89 heparin are unlikely to pose a risk of heparin overdose; however, these devices should also  
90 comply with the recommendations in this guidance.  
91

## 92 **3. Background**

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94 Heparin has been identified as a high-alert medication by the Institute for Safe Medication  
95 Practices (ISMP) due to a heightened risk of patient harm when dosed incorrectly. In 2003, the  
96 USP's Safe Medication Use Expert Committee recognized a recurring trend of medication errors  
97 related to misinterpretation of the expression of concentration on the labeling of injectable  
98 products, resulting in serious consequences to patients, including death. Heparin products span a  
99 wide range of doses and concentrations based on the indication for use for the product as well as  
100 the intended patient population. Heparin administration for systemic anticoagulation is provided  
101 as final concentrations ranging from 50-100 units/mL. The source vials from which these  
102 dilutions are prepared contain concentrations ranging from 1,000-20,000 units/mL. When  
103 heparin sodium is only intended to maintain patency of an indwelling intravascular catheter, the

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<sup>4</sup> The Agency updates guidances periodically. To make sure you have the most recent version of this guidance, check the CDER guidance page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

<sup>5</sup> Some devices for in vitro diagnostic uses include heparin. Products that include a device and heparin for in vivo use are combination products. Center assignment for combination products is based on which constituent part (the drug or device in this case) provides the primary mode of action (PMOA), i.e., makes the greatest contribution to the overall intended therapeutic effects of the combination product. See 21 CFR 3.2. Combination products that include heparin and a device are assigned to CDRH if the device provides the PMOA.

104 heparin lock flush solution (which is regulated by FDA as a drug-device combination product  
105 with a device primary mode of action (see 71 FR 47499, August 17, 2006)), typically includes  
106 heparin concentrations ranging from 1-100 units/mL packaged in 1-30 mL vials with total drug  
107 content ranging from 1 unit to 1,000 units or a variety of fill volumes in prefilled syringes with  
108 total drug amounts per syringe ranging from 1 unit to 500 units.

109  
110 In 2007, the USP Parenteral Products-Industrial Expert Committee recommended revisions to the  
111 new "Strength and Total Volume for Single- and Multiple-Dose Injectable Drug Products"  
112 section of USP General Chapter <1> *Injections*.<sup>6</sup> These revisions became official in 2009. This  
113 chapter directs that the strength per total volume should be the primary and prominent expression  
114 on the principal display panel of the label, followed in close proximity by strength per mL  
115 enclosed by parentheses. Following these changes, FDA and ISMP expressed concern that the  
116 labeling prescribed in the Heparin Lock Flush Solution monograph (and in the Heparin Sodium  
117 Injection monograph) does not conform with the requirements in General Chapter <1>  
118 *Injections*. USP's Expert Committees, including the committee responsible for these Heparin  
119 monographs, Monographs-Biologics and Biotechnology 1, proposed revisions to the labeling  
120 sections of the heparin monographs that will require the product container labels to comply with  
121 the USP standards for injectable medications, specifically, General Chapter <1> *Injections*.  
122 Those revisions became official May 1, 2013.

123

## 124 4. Labeling Statements

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### 126 A. For Heparin Lock Flush Solution Products

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128 The USP monograph for Heparin Lock Flush Solution requires the product labels<sup>7</sup> express  
129 strength per total container volume as the primary expression of strength, followed in close  
130 proximity by strength per mL enclosed by parentheses, for single- and multiple-dose injectable  
131 drug products. The strength per total volume should be the primary and prominent expression of  
132 the principal display panel of the label.<sup>8</sup> For example:

133

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

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137 For products containing a volume of less than 1 mL, the strength per fraction of an mL should be  
138 the only expression of strength.<sup>9</sup> For example;

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<sup>6</sup> USP has announced plans to relocate this information to General Chapter <7> *Labeling* in the near future ([http://www.gphaonline.org/media/cms/Donna\\_Bohannon.pdf](http://www.gphaonline.org/media/cms/Donna_Bohannon.pdf)).

<sup>7</sup> Under section 201(m) of the FD&C Act, labeling means all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article. 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, 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.

<sup>8</sup> USP37-NF32, at 3228 (Heparin Lock Flush Solution).

<sup>9</sup> Id.

140 Strength/mL: 100 USP Units /0.5 mL

141  
142 The Agency further recommends that the above information be included in the instructions for  
143 use as part of the device/combination product description. Consistent with the monograph, the  
144 label must identify the organ (e.g., intestinal mucosa) and the animal species (e.g., porcine) from  
145 which the heparin sodium is derived.<sup>10</sup>

146  
147 B. For Heparin-Bonded Products

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149 For heparin-bonded products, the total amount of heparin per total surface area should be  
150 displayed on the primary package label followed by the concentration per area unit in  
151 parentheses. For example:

152  
153 Total amount of heparin/total surface area: 100 USP Units /total surface area<sup>2</sup>  
154 Strength/area unit: (10 USP Units)/unit of surface area<sup>2</sup>

155  
156 The Agency further recommends that the above information be included in the instructions for  
157 use as part of the device/combination product description, and that the labeling identify the tissue  
158 (e.g., intestinal mucosa) and the animal species (e.g., porcine) from which the heparin sodium is  
159 derived.

## 160 161 **5. Safety Testing for Heparin-Containing Products**

162  
163 Manufacturers of Heparin Lock Flush Solution must comply with the current USP monograph  
164 for that product, as well as the USP drug substance monograph for Heparin Sodium.  
165 Manufacturers of Heparin Sodium Injection must comply with the current USP monograph for  
166 that product, as well as the USP drug substance monograph for Heparin Sodium. See sections  
167 501(b) and 502(g) of the FD&C Act. Firms are also recommended to follow the guidance  
168 document, *Heparin for Drug and Medical Device use: Monitoring Crude Heparin for Quality*,  
169 mentioned above.<sup>11</sup> In addition, we recommend that manufacturers who receive heparin sodium  
170 drug substance or active pharmaceutical ingredient (API) that is represented to be “USP” to  
171 produce a combination product or an in vitro diagnostic medical device that includes heparin  
172 sodium or low molecular weight heparin ensure and document that the heparin has been tested  
173 according to the current USP drug substance monograph, and that it is manufactured and/or  
174 tested consistent with applicable guidance documents on heparin. Manufacturers of medical  
175 devices and combination products which include heparin must comply with the elements of  
176 safety testing that are required to be performed and documented as part of compliance with the  
177 Quality System (QS) regulation for devices, and with both the QS regulation and current good  
178 manufacturing requirements for drugs if the product is a combination product (see 21 CFR Part  
179 4).

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<sup>10</sup> Id.

<sup>11</sup> In addition, the Center for Drug Evaluation and Research (CDER) has issued a draft guidance for industry, [Immunogenicity-Related Considerations for the Approval of Low Molecular Weight Heparin for NDAs and ANDAs](http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm392194.pdf), available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm392194.pdf>. When final, this guidance will represent the agency’s current thinking on this topic.

180  
181 Premarket submissions to CDRH – premarket notification (510(k)) submissions, premarket  
182 approval (PMA) applications, *de novo* requests, and humanitarian device exemption (HDE)  
183 applications – should describe the heparin product in detail and document compliance with  
184 heparin safety testing. Please note, however, that heparin testing data and records should be  
185 maintained on file with the medical device or combination product manufacturer, but do not need  
186 to be included in premarket submissions. See Appendix A for more details. The premarket  
187 submission should include the following information:

- 188
- 189 • Heparin source-tissue and species (e.g., porcine intestinal mucosa);
  - 190
  - 191 • Confirmation of the species origin of heparin sodium (e.g., porcine);
  - 192
  - 193 • Identification of the actual manufacturer (i.e. name, address and contact information) of  
194 the heparin sodium API and any repackers and distributors who handle the heparin  
195 sodium before receipt.
- 196

197 The premarket submission should also provide the following to indicate the manufacturer’s  
198 conformance with testing parameters from the guidance [Heparin for Drug and Medical Device  
199 Use: Monitoring Crude Heparin for Quality](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291390.pdf)  
200 ([http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/  
201 UCM291390.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291390.pdf))<sup>4</sup>:

- 202
- 203 • Testing for OSCS using methods that are qualified and suitable for detecting low levels  
204 of OSCS concentrations (e.g., strong anion exchange high-pressure liquid  
205 chromatography and <sup>1</sup>H Nuclear Magnetic Resonance).
  - 206
  - 207 • Heparin-containing combination products and medical devices should also comply with  
208 the contaminant safety testing recommendations in the USP monograph on Heparin  
209 Sodium and CDER’s guidance recommendations to detect OSCS contamination of  
210 heparin and for identification of the animal origin of the heparin.

## 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 Q7*).
  - Description of how the manufacturer followed CDER's heparin guidance, [Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291390.pdf) (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291390.pdf>).
  - Although batches of Heparin Sodium that have deviated, failed or 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.