October 2, 2015

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852


Dear Sir or Madam:

The Advanced Medical Technology Association (“AdvaMed”) is pleased to provide comments on FDA’s draft guidance “Heparin-Containing Medical Devices and Combination Products: Recommendations for Labeling and Safety Testing; Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders.”

AdvaMed represents manufacturers of medical devices, diagnostic products, and health information systems that are transforming health care through earlier disease detection, less invasive procedures, and more effective treatment. Our members range from the smallest to the largest medical technology innovators.

While the draft guidance clarifies important details concerning these devices, there are several distinctions that must be made. Our specific comments on the document are provided in Attachment 1.

Respectfully submitted,

/s/
Sharon A. Segal, Ph.D.
Vice President
Technology and Regulatory Affairs

Attachment
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<th>Line(s) No.</th>
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| 87-90       | Revise to read as follows:  
Products that only include coatings containing permanently bonded heparin sodium or low molecular weight heparins with a fixed total dose of heparin are unlikely to pose a risk of heparin overdose; however, these devices should also comply with the recommendations in this guidance. | Products with coatings containing covalently (permanently) bonded heparin sodium or low molecular weight heparins are not intended to, and do not, provide a dose of heparin to the circulating blood. The action of the bonded heparin is localized at the surface of the device and does not act systemically. No dose of heparin is provided. For this reason, the statement “with a fixed total dose of heparin” in reference to products with coatings containing permanently bonded heparin sodium or low molecular weight heparins is not appropriate and should be removed. See the comment below for lines 147-159 of the guidance regarding the nominal maximum total amount of heparin (USP units) released systemically per product per unit time. |
| 89          | Remove the devices from scope that contain heparin in the coatings that are not intended to leach | FDA acknowledges that the risk of overdose is low. |
| 135; 154    | It is not clear whether there is a measurement tolerance (e.g., +/- 15%) or if this supposed to be a maximum concentration only. | Rationale |
| 147-159     | Revise to read as follows:  
B. For Heparin-Bonded Products intended for release of heparin  
For heparin-bonded products intended for release of heparin expressing activity in surrounding body fluid, the total amount strength of heparin per total surface area should be displayed on the primary package label followed by the concentration per area unit in parentheses.  
Total amount strength of heparin/total surface area: 100 USP Units/total surface area²  
C. For Heparin-Bonded Products with covalently/permanently bonded heparin  
For products with permanently bonded heparin, not intended to act by releasing heparin, information on drug strength is not relevant.  
The Agency further recommends that the above information be included in the device/combo product labeling (IFU or label), and that the labeling identify the tissue (e.g., intestinal mucosa) and the animal species (e.g., porcine) from which the heparin was derived.  
| The proposed changes to lines 147-159 of the guidance are intended to correlate the information in Section 4.B. Heparin-Bonded Products with the following information provided in Section 2. Scope (lines 87-90) of the guidance, which states:  
Products that only include coatings containing permanently bonded heparin sodium or low molecular weight heparins are unlikely to pose a risk of heparin overdose; however, these devices should also comply with the recommendations in this guidance.  
Currently, there are two methods that are used to bind heparin to a product surface:  
1. Covalently or permanently bound (e.g., CARMEDA® BioActive Surface)  
2. Non-covalently bound or releasable (ionic bonded, impregnated in a collagen matrix, etc.)  
The guidance is intended to provide information to clinicians in product labeling in order to reduce the risk of systemic heparin overdose. For this reason, it is important to understand how heparin that is applied to a product surface (see #1 and 2 above) is bound to the surface.  
The “amount” of heparin indicates mass of heparin in contrast to “strength” or “potency” of heparin. Therefore it is suggested to use the
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<td>heparin sodium is derived.</td>
<td>term strength only when dealing with devices releasing heparin. “Strength” in term of USP units is relevant, and defined, when taking place in a solution allowing for diffusion as compared to the “amount” of heparin. This is why this is relevant only for products intended to release bonded heparin. Information on the total strength of heparin from a product with a heparin-releasing surface will be relevant to clinicians so that they can use this information to determine the total amount of systemic heparin that patients receive. Labeling by strength in USP units lacks clinical relevance for products with permanently bound heparin. It is therefore suggested to divide bonded products into two different classes (Sections 4.B and 4.C in suggested new text). The recommendation in lines 157-159 of the guidance that device/combination product labeling identify the tissue (e.g., intestinal mucosa) and the animal species (e.g., porcine) from which the heparin sodium is derived should be deleted since this requirement applies to heparin API (as stated in the USP monograph) and does not apply to heparin-containing medical devices and combination products.</td>
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<td>149</td>
<td>Delete, or include in IFU with some information on how the amount of heparin is determined</td>
<td>It is stated that the “amount” of heparin per unit area be provided on the primary package label but FDA has provided no validated or approved methodology by which to conduct the assessment. The established Anti-Xa and Anti-IIa assays within the USP monograph for heparin sodium are validated using “free” heparin in solution, and are not immediately transferable to the measurement of immobilized heparins. A lack of consistent and defined methodology will lead to inconsistent practice and valuation of heparin potency across various manufacturers’ product lines. If potency labeling is required for immobilized and non-eluting heparin products, the agency should provide acceptable methodology through which manufacturers may standardize their measurements.</td>
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<td>163-166</td>
<td>Revise to read as follows:  Manufacturers of Heparin Lock Flush Solution 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 Injection must comply with the current USP monograph for that product at the time of</td>
<td>Heparin and low molecular weight heparin can have a shelf life up to four or more years. When the API is first received by the combination product manufacturer, it is inspected to ensure conformance to the current USP drug substance monograph at that time. Any changes in the USP heparin monographs would not necessarily make prior heparin API unacceptable for use in a combination product since testing to the prior USP monograph demonstrated compliance at the time of</td>
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| 169-174    | *manufacture, as well as the current USP drug substance monograph for Heparin Sodium that was in place at the time of manufacture of the heparin sodium drug substance or active pharmaceutical ingredient (API).*  

Revise to read as follows:  

*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 USP drug substance monograph that is current or in place at the time of manufacture of the API, and that it is manufactured and/or tested consistent with guidance documents on heparin that were current or in place at the time of manufacture of the API. Since the API was found to meet the current USP monograph at the time of manufacture, re-testing of heparin sodium or low molecular weight heparin to demonstrate conformance to revisions or updates of the USP monograph after API manufacture is not required.*  

Heparin sodium and low molecular weight heparin can have a shelf life up to four or more years. When the API is first received by the combination product manufacturer, it is inspected to ensure conformance to the current USP drug substance monograph at that time. Any changes in the USP heparin monograph would not necessarily make prior heparin API unacceptable for use in a combination product since testing to the prior USP monograph demonstrated compliance at the time of manufacture.