Heparin Market Report

Background
Heparin is an injectable anticoagulant, which is a compound used to prevent blood clotting. Heparin is widely used clinically in practices like dialysis (370,000 patients/year), deep vein thrombosis (DVT) treatment (900,000 patients/year), flushing IVs and central lines, and most cardiac surgeries. Cardiac surgery represents one of the largest groups with over half a million surgeries being performed annually. Heparin is used in one of two forms, unfractionated heparin (UH) or low molecular weight heparin (LMWH). While heparin is a valuable drug, improper use can cause severe hemorrhaging (bleeding out). When this happens, the options are to wait for the heparin to wear-off or administer an antidote. UH has a half-life of about 1-2 hours, can be reversed by using protamine sulfate over a period of four hours. LMWH, however, has a half-life of 4-5 hours and generally does not respond to reversal via protamine sulfate. LMWH is also the most preferentially used compound with children.

Risk associated with heparin use
The FDA receives approximately 400,000 reports of adverse drug events per year. In a study analyzing 300,000 events occurring in 2005, 3.6% (approx. 11,000 events in one year) were related to heparin, and harm was caused in 275 cases. Between 2007 and 2008, heparin use caused 246 deaths, 149 of which were from an allergic reaction. In 36% of cases, the error was due to the wrong dose or quantity, where 18% of the time the error was an overdose of 100x or more. When this error happens with LMWH, there is not a good antidote so many times the care provider can only wait for the effects to wear off, which can 5+ hours.

The estimated cost of these heparin related errors is approximate $150M/year, but this number is likely very low. Annually the US spends $4.2B a year due to medical errors, and 3.6% of these errors are related to heparin, however heparin mistakes tend to be much more costly than say mistakes with less risky medications. According to Grissinger et al. in the Joint Commission Journal on Quality and Patient Safety “Anticoagulants are among the most frequently cited product classes involved in harmful medication errors”. The article further states, “review of all anticoagulant errors showed that anticoagulants accounted for 1.72 medication errors per 10,000 patient days.”

The product – Removal of heparin from patient blood and/or the quantification of heparin in medical samples.
The HB tag would be immobilized on a functionalized membrane for the direct removal of heparin from blood. This technology could be sold to medical membrane manufacturers like Medtronic or Cole-Palmer. Additionally, antibodies to the HB tag could be used to develop a quantitative rapid ELISA for blood heparin concentration.

The Need
The HB tag, with its ability to bind heparin, could be immobilized on a membrane or other stationary phase for use in clearing heparin from blood or monitoring levels of heparin in dialysis patients. This specifically could be used in the treatment of acute heparin overdose. Currently, acute heparin overdose is treated with the drug protamine sulfate. This drug is also used routinely to negate the effects of heparin when used during cardiac surgery when the patient is placed on bypass. However, protamine has been reported to cause allergic reactions in patients who are allergic to fish. These patients must be pretreated with
antihistamines and steroids prior to injection of protamine and anaphylaxis is still a risk. Common side-effects also include a sudden drop in blood pressure, bradycardia, pulmonary hypertension, and dyspnea. Additionally, the half-life of protamine is much shorter than heparin, causing multiple doses to be necessary. According to Figueiredo et al. “Reversing heparin-induced anticoagulation quickly and effectively can be challenging in bleeding patients undergoing emergency surgery. The required dose of protamine to neutralize unfractionated heparin (UFH) is difficult to predict and use of standard coagulation tests such as activated partial thromboplastin time (aPTT) to assess the effectiveness of reversal may delay surgery, compromising patient safety.” However, there are currently assays available to measure both unfractionated heparin and low molecular weight heparin in blood. It is important to note, that in the case of acute heparin overdose, there is currently no way to remove the heparin, the only option is to provide an antidote. Heparin is also frequently used in the Neonatal Intensive Care Unit (NICU). According to Arimura et al., during 2006 and 2007 nine neonates received potentially fatal doses of heparin.

Market Area and Barriers

The global medical device market is estimated to reach $440 Billion by 2018⁷, with the dialysis instrumentation market estimated to reach $83.21 Billion by 2018⁸. The biggest hurdle will be the approval of the membrane by the FDA as a medical device, a 510(k) process. This risk will be reduced somewhat in that it will be considered similar to already approved dialysis membranes and/or heart-lung bypass machines.
**Product 3 – removal and quantification of heparin for medical purposes**

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| Currently there is not a way to remove heparin from a patient in the case of overdose. Additionally, there is not a rapid way to determine how much heparin is in the blood | Use HB tag with functionalized membranes. Develop a rapid test for heparin | High specificity to heparin and not other blood products | Would be the only membrane on the market to remove heparin | Licensees  
Medtronic  
Medical device manuf.  
End users  
Doctors  
Surgeons  
Dialysis Clinics  
Hospitals |

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<th><strong>KEY METRICS</strong></th>
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| FDA allowance of medical device  
Heparin test would need to be quantitative | Conferences  
Success of rapport created through ph calls  
Word of mouth and subsequent success of sample product | Production Cost (Material, Technical Expertise, Facilities used)  
One time production set up cost  
Trials has to be done. Product CANNOT fail (@ higher cost?)  
FDA validation required | Product sale  
License Agreements |
Commercialization Feasibility Study

The ability to rapidly clear heparin from blood during dialysis or heart-lung bypass could potentially hold value to the medical field, particularly in the case of neonatal over-dose. While overdose in adult patients is critical, overdose in neonatal patients is often fatal. Conversations with Dr. Jiunn Teo, senior scientist at Fresenius Medical Care (FMC) reinforced the potential value of the HB tag. He indicated that heparin is always used in conjunction with dialysis treatment, which is performed on average 3x per week for a patient. This frequency of use means that knowing heparin blood levels and having an easy way to remove it could be valuable.