

## Heparin Formulation: New Standards of Units

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Heparin is a naturally occurring anticoagulant that has been used for over 70 years. It is clinically used for the prevention of venous thrombosis and for the immediate and acute treatment of venous thrombosis, the management of acute coronary syndrome, and for the prevention of blood clotting during interventional procedures and surgery. Because of the risk of bleeding with an overdose, and the risk of thrombosis with sub-therapeutic dosing, heparin needs to be monitored.

With the recent issue on the contamination of heparin with over-sulfated chondroitin sulfate, the US Pharmacopeia (USP) revised the heparin monograph to include the current knowledge and assay techniques to enhance the identification of the heparin product as well as to detect impurities.

In addition to the above improvements in the USP heparin monograph, the assays to determine the biological activity of heparin were also revised to include the modern assays. The biological assays require the use of a reference standard (RS) to determine potency.

In 1973 the USP established a heparin RS with unitage that differed from the International Standard for heparin issued by the WHO. The difference between the two was about 10%. In 2009, coincident with the heparin monograph revisions, the current USP heparin RS was in short supply and a new RS needed to be established. In the interest of globalization, the USP made the decision to conform to the WHO heparin unit definition.

The FDA notified healthcare professionals that effective October 1, 2009 the USP had adopted a new potency assay for heparin and a new potency reference standard. Together these changes resulted in a new USP unit definition for heparin that would be 10% lower than for past heparins. This would affect all heparins manufactured in the US and Canada.

We at the Loyola University Medical Center undertook an investigation to determine if there were significant differences in anticoagulant activity between the heparin standardized by the old RS and the heparin standardized by the new RS.

This study was carried out prior to the clinical release of the new heparin. Thus it was possible only to perform an in vitro study using freshly collected citrated plasmas from male and female healthy volunteers.

This comparison revealed that in all assays [clot-based aPTT, Heptest and ACT, as well as the chromogenic (colorimetric) anti-FXa and anti-FIIa (anti-thrombin) assays], the new lot of heparin had a significantly lower anticoagulant activity.