Branded Enoxaparin and a US Generic Version: Differences in Potency and Sustainability of the Antithrombotic Effect
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Purpose
Low molecular weight heparins (LMWHs) are biologically derived drugs, composed of a heterogeneous mixture of oligosaccharides. LMWHs mediate their antithrombotic property through anti-FXa and anti-thrombin (anti-FIIa) activities via antithrombin (AT) as well as a spectrum of other biological activities. LMWHs are proven effective and well-tolerated in various clinical settings, including prevention and treatment of venous thromboembolism and in the management of acute coronary syndrome. In the US, the branded-originator enoxaparin (Lovenox®; Sanofi US) is approved in these indications. Generic versions of enoxaparin have now been approved in the US through an abbreviated pathway, thus allowing for their use in all indications as the branded-originator.

Methods
Studies conducted in primates (Macaca mulatta) comparing the biological activities of branded with one generic enoxaparin (Sandoz US) [Clin Appl Thromb/Hemost 2012:19(3):261] using five batches of each product showed significant differences in pharmacodynamic behaviors, particularly in the mean release of tissue factor pathway inhibitor (TFPI). In order to further investigate these differences, TFPI levels as a function of time and anti-FXa or anti-FIIa activity were ascribed to an indirect validated response model with a tolerance component. A non-linear mixed effect modeling was used [software program NONMEN (version 7.2)] and the influences of covariates (branded or generic) on all pharmacodynamic parameters were tested.

Results
The TFPI values were increased by both administrations of branded and generic enoxaparins but the values were different and the effect was significantly described when using separate values of the slope for anti-FXa and anti-FIIa stimulation of TFPI release: anti-FXa branded vs generic respectively [mean (relative standard error %)] 0.20 (21) vs 0.13 (31) (p < 0.001) and anti-FIIa branded vs generic respectively 1.22 (42) vs 0.65 (49) (p < 0.001).

Conclusion
The observed differences between products may be due to compositional differences in the oligosaccharide components of the drugs in blood circulation at a given time. These findings suggest that product characterization to determine bioequivalence and thus clinical interchangeability of a generic LMWH is more complex than simple anti-FXa and anti-FIIa measurements and the chemical characterization that is required at this time.