

## Assessment of the Mixing Efficiency of Neutral Protamine Hagedorn Cartridges

Pia Kaiser, M.Sc.,<sup>1</sup> Sebastian Maxeiner, M.Sc.,<sup>1</sup> Alexander Weise, M.Sc.,<sup>1</sup> Florain Nolden, M.Sc.,<sup>1</sup>  
Anja Borck, M.D.,<sup>2</sup> Thomas Forst, M.D.,<sup>1</sup> and Andreas Pfützner, M.D., Ph.D.<sup>1</sup>

### Abstract

Reliable application of neutral protamine Hagedorn (NPH) insulin requires previous resuspension of the suspension by tipping over the cartridge 20 times. This procedure is considered annoying by patients. The goal of this investigation was to assess the efficiency of the mixing procedure when performed less frequently than recommended. Neutral protamine Hagedorn insulin cartridges from five different manufacturers (sanofi-aventis, Lilly, Berlin-Chemie, B. Braun, and Novo Nordisk) were emptied with doses of 28 IU in the morning and the evening over 5 days. While the first dose was obtained after a regular resuspension procedure (20× tipping over), the consecutive doses were obtained after 3, 6, 10, or 20 mixing procedures (12 cartridges per experimental series, two doses/day). Insulin concentrations of doses 1, 2, 6, and 10 were determined by high-pressure liquid chromatography. Between dosing, cartridges were stored at room temperature in a horizontal position. Comparable insulin concentrations were seen in the first correctly prepared doses. Pronounced and substantial deviations from the selected dose were observed with most of the cartridges, in particular when resuspending only 3 and 6 times. Mean absolute percentage deviations when tipping 3 times and maximally observed overdoses were: Insuman basal:  $1.1 \pm 1.0\%/4$  IU, Humulin N:  $2.6 \pm 3.4\%/19$  IU, Berlinsulin H basal:  $4.4 \pm 6.0\%/26$  IU, Insulin B. Braun basal:  $10.4 \pm 8.9\%/38$  IU, and Protaphane:  $4.7 \pm 4.1\%/19$  IU (all  $p < 0.05$  vs Insuman basal). Only one cartridge with three metal mixing bullets (sanofi-aventis) was resuspended efficiently with only a few mixing procedures. All other cartridges with fewer bullets were shown to deliver potentially harmful doses if used for treatment when the mixing procedure was less frequent than demanded in the instructions for use.

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**Author Affiliations:** <sup>1</sup>IKFE, Institute for Clinical Research and Development, Mainz, Germany; and <sup>2</sup>Sanofi-aventis, Berlin, Germany

**Abbreviations:** (HPLC) high-pressure liquid chromatography, (NPH) neutral protamine Hagedorn, (USP) United States Pharmacopeia

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**Corresponding Author:** Andreas Pfützner, M.D., Ph.D., IKFE-Institute for Clinical Research and Development, Parcusstr. 8, D-55116 Mainz, Germany; email address [AndreasP@ikfe.de](mailto:AndreasP@ikfe.de)